

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 31/43, 31/545		A1	(11) International Publication Number: WO 92/15299
(21) International Application Number: PCT/US92/01405		(43) International Publication Date: 17 September 1992 (17.09.92)	
(22) International Filing Date: 3 March 1992 (03.03.92)		(74) Agents: BLOOM, Leonard et al.; 401 Washington Avenue, Suite 905, Towson, MD 21204 (US).	
(30) Priority data: 664,795 5 March 1991 (05.03.91) US		(81) Designated States: AT (European patent), AU, BE (European patent), BR, CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent).	
(71) Applicants: BLOOM, Leonard [US/US]; 401 Washington Avenue, Suite 905, Towson, MD 21204 (US). TOWSEND, Marvin, S. [US/US]; 8 Grovepoint Court, Rockville, MD 20854 (US).		Published <i>With international search report.</i>	
(71)(72) Applicants and Inventors: ROBINSON, Howard, N. [US/US]; 18 Hickory Knoll Court, Lutherville, MD 21093 (US). MARTIN, Neil, F. [US/US]; 7201 Loch Edin Court, Potomac, MD 20854 (US).			

(54) Title: TOPICAL TREATMENT OF ACNE

(57) Abstract

The object of the invention is to provide methods and compositions for topically treating acne and acneiform dermal disorders by applying to the skin an amount of an antibiotic selected from the group consisting of ampicillin, amoxicillin, other aminopenicillins, and cephalosporin, and derivatives and analogs thereof, effective to treat the acne and acneiform dermal disorders. The antibiotic is blended with a carrier suitable for topical application to dermal tissues. The carrier includes at least one carrier ingredient selected from the group consisting of water and a water-miscible alcohol, wherein combined weight percents of said carrier ingredients is in a range spanning 3 % to 99.5 %.

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	ML	Mali
AU	Australia	FR	France	MN	Mongolia
BB	Barbados	GA	Gabon	MR	Mauritania
BE	Belgium	GB	United Kingdom	MW	Malawi
BF	Burkina Faso	GN	Guinea	NL	Netherlands
BG	Bulgaria	GR	Greece	NO	Norway
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IE	Ireland	RO	Romania
CA	Canada	IT	Italy	RU	Russian Federation
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark	MG	Madagascar		

TOPICAL TREATMENT OF ACNECross-Reference to Related Application

The present application is based on U.S. patent application of the same inventors, Robinson et al, Ser. No. 07/664,795, filed on March 5, 5 1991, for TOPICAL TREATMENT OF ACNE.

Technical Field

The present invention relates to the field of treating the skin condition known as acne. More specifically, the present invention is concerned 10 with the prophylactic or therapeutic topical treatment of acne. Even more specifically, the present invention is concerned with the topical treatment of such skin disorders as acne vulgaris, other acneiform dermal conditions, e. g. 15 preadolescent acne, acne rosacea (now known as rosacea), premenstrual acne, acne venenata, acne cosmetica, pomade acne, acne detergicants, acne cosmetica, acne excoriée, gram negative acne, steroid acne, acne conglobata, or nodulocystic 20 acne. The present invention can also be used for topically treating certain types of dermatitis, e. g. perioral dermatitis, seborrheic dermatitis, gram negative folliculitis, sebaceous gland dysfunction, hidradenitis suppurativa, pseudo- 25 folliculitis barbae, or folliculitis.

Art

Acne vulgaris is a common disease which afflicts approximately 90% of all teenagers, and, not uncommonly, affects men and women in their 30 twenties or thirties or may persist in adults for many years. Acne vulgaris most commonly occurs on oily areas of the skin with high sebaceous gland concentration. The areas of high sebaceous gland

-2-

concentration are the face, ears, retroauricular areas (e. g. behind the ears), chest, back, and occasionally the neck and upper arms.

Acneiform eruptions can occur wherever there
5 is a pilosebaceous unit or sebaceous follicle
which does include the entire surface of the skin.

The basic lesion in acne is the comedo commonly known as the blackhead. The comedo is created by retention of layers of dead skin known
10 as keratin in the lining of the follicles. In additions to hyperkeratosis (which is thickening or retentative layering of keratin), there is an accumulation of sebum which is the lipid-laden product of the sebaceous gland. The cells of the
15 sebaceous glands in which sebum originates are the sebocytes. The combination of the keratin and the sebum produces a plugging of the mouth or opening of the follicular canal, and papules are formed by inflammation around the comedones (plural of
20 comedo). Depending upon the degree of inflammation, pustules, cysts, nodules, granulomatous reactions, scars, and keloids may develop. Most typical forms of mild acne vulgaris demonstrate the predominance of comedones
25 with the occasional pustules. Pustules and papules predominate in more severe cases. These can heal with scar formation; that is, fibrosis of the lesions which are deep and penetrating. In moderately active cases, larger cystic lesions
30 can develop.

Acne vulgaris can appear in many clinical varieties. The mildest case manifests comedones on oily skin and is called acne comedo.

-3-

Papular acne is another variety of acne which has many inflammatory papules. This form of acne is common in adolescent skin, but it can be seen in all ages. The papular inflammatory form of 5 acne can progress to an indurated, deeper, and destructive form known as acne indurata. These lesions can produce severe scarring and can be quite deep seated and destructive.

Steroid acne vulgaris can occur when oral 10 corticosteroids or topical steroids are used and occurs as inflammatory follicular papules. When oral corticosteroids are ingested, the inflammatory papules are usually sudden in appearance and can cover the chest, back, arm, and 15 face. When topical corticosteroids are used for more than two weeks, a localized inflammatory papular response can develop which can proceed to a granulomatous chronic reaction known as steroid acne rosacea.

20 Premenstrual acne can occur in a large number of menstruating women as a papular and pustular acne vulgaris, approximately one week prior to menstruation. There is a body of evidence that implicates a surge in progesterone as the mediator 25 of premenstrual acne.

Preadolescent acne is divided into neonatal, infantile, and childhood forms of acne. The 30 neonatal form is limited to the first few weeks of life. It usually develops a couple of days after birth. It more commonly afflicts males and reveals transient facial papules and pustules which can clear spontaneously in a few days or weeks. The stimulation of neonatal sebaceous glands by circulating maternal progesterone 35 appears to be the cause.

-4-

If the acne persists beyond the first month of life, the acne is called infantile acne and can extend into childhood, adolescence, and adult life. The childhood acne can result from a 5 persistent infantile acne or can develop de novo after age two. This form of acne is uncommon, but it has more of a male predilection. It is characterized by comedones commonly in groups, papules, pustules, and, rarely, cysts. This 10 condition can extend from a few weeks to several years and can develop into pubertal acne.

Acne venenata is by definition a comedonal or papular acne which occurs after exposure to chlorinated hydrocarbons (chloracne), cutting 15 oils, petroleum oil, coal tar, and pitches. Acne cosmetica is a persistent low grade comedonal and/or papular and pustular acne that occurs usually on the chin and cheeks of adult women due to oil-based cosmetics, i. e. foundations, facial 20 creams, and sunscreens.

Pomade acne is a type of acne cosmetica which appears to occur almost exclusively in black persons who apply grease and oil to scalp hair and the face as a grooming aid. The lesions are 25 predominately comedonal acne and can develop into inflammatory acne papules, depending upon the chronicity of the pomade use.

Acne detergicans occurs as a type of comedonal acne in patients who use oil-based 30 cleansing soaps. Acne excoriée, also known as pickers acne, starts out as mild form of papular or comedonal acne which is manipulated or picked and causes further inflammation, more papules, and sometimes scars, pitting, and atrophy of the skin.

-5-

- Gram negative acne, sometimes called gram negative folliculitis when it extends to the neck, arms, legs, and truck, is a form of an inflammatory papular, follicular, and pustular response to gram negative organisms including *Enterobacter*, *Klebsiella*, *Escherichia*, *Proteus*, *Serratia*, and *Pseudomonas*. The most characteristic lesion on the face is superficial pustules, or papulo-pustules (which is a combination of a papule and pustule). The face can show diffuse erythema and inflammation surrounding these pustules and juicy papules or papulo-pustules. The gram negative acne is usually highly resistant and usually occurs in patients who have bad inflammatory papular acne for long periods or who have been treated with long term oral administration of antibiotics such as tetracycline, erythromycin, or minocycline or topical antibiotics such as topical clindamycin or topical erythromycin. Subsequent to the oral administration of tetracycline or erythromycin, oral administration of amoxicillin, ampicillin, and trimethoprim-sulfomethoxazole has been shown to be effective in treating this disease. (Poli, F., Prost, C., Revuz, J., Gram-negative Folliculitis, Ann. Dermatol. Venereol., 115:797-800, 1988).
- In another reference, Marks, R. and Ellis, J., "Comparative effectiveness of tetracycline and ampicillin in rosacea", *Lancet*, 1971, vol. 2, pages 1049-1052, there is a disclosure that ampicillin has been used orally for treatment of rosacea. More specifically, orally administered ampicillin was compared with orally administered tetracycline in the treatment of rosacea.

-6-

Furthermore, in the personal experience of one of the inventors, in his capacity as a practicing dermatologist, in treating well over 200 patients, that oral ampicillin taken in the 5 form of an oral capsule between 500 mg and 1 gm each day for one month greatly improves this condition. Before treatment with ampicillin orally, the patients appear to have inflammatory papules and pustules present, and treatment of 10 this clinical subset of acne vulgaris appears to have good success with the oral ampicillin.

However, unwanted side effects often occur with the oral administration of ampicillin (and amoxicillin). For example, unwanted side effects 15 from oral administration often include diarrhea, cramping, and nausea. It would be desirable, therefore, to provide a treatment with ampicillin (and amoxicillin) which does not result in the unwanted side effects stated above.

20 Acne rosacea is an inflammatory eruption that is chronic and occurs on the face, especially on the nose as well as the scalp and neck, in some instances. It is manifested by erythema, pustules, papules, telangiectasia (which is 25 dilation of superficial capillaries), and hypertrophy of sebaceous glands. The middle portions of the face are most frequently involved. The eyes and eyelids are not uncommonly involved and can produce inflammation and infection of the 30 conjunctiva, eyelids, and hypertrophy of the meibomian glands. Acne rosacea is often called simply rosacea and is most common in middle aged women and men. Rosacea can go on to form a granulomatous rosacea which is characterized by

-7-

resistant inflammatory papules which when biopsied reveal noncaseating epithelial cell granulomas.

Pseudofolliculitis barbae is a predominantly male affliction which is characterized by

- 5 inflammatory papules and pustules on the bearded area of the face most commonly in black persons, but all racial groups can be affected. The mechanism is thought to be an inflammatory response to the end of hair (usually curly beard
- 10 facial hair) into the skin causing a foreign body inflammatory response.

Folliculitis is an inflammatory reaction around the hair follicle which can be bacterial or nonbacterial in nature. Predominately,

- 15 folliculitis is caused by gram positive organisms such as Staphylococcus and Streptococcus, and less frequently by gram negative bacteria discussed hereinabove with respect to gram negative folliculitis.

- 20 Perioral dermatitis is a common papular inflammatory eruption which is confined around the mouth. It most commonly afflicts women in their early twenties to middle thirties, but it can be seen in adolescents and more mature adults.

- 25 Hidradenitis suppurativa is a suppurative (chronic) and cystic disease of apocrine gland regions of the skin, including the axillae, perineal region and groin.

- 30 There is a genetic tendency to acne, in particular acne conglobata which is a deep cystic and sinus forming type of acne. This condition is essentially a deep, aggressive form of cystic acne occurring in the apocrine gland regions. Topical administration of clindamycin has been used to
- 35 treat this form of cystic acne.

-8-

The etiology of acne vulgaris and related disorders as discussed above is not completely known in every detail. However, what is known is that acne, in general, is caused by a plurality of 5 factors. In general, there are four main factors that cause acne: genetics; hormonal activity; bacteria; and the inflammatory response.

Genetics is a prominent component as it is well known that several members of the same family 10 can be affected with moderate to severe scarring acne. The inheritance by some is thought to be autosomal dominant, but this has not been definitively proven. Furthermore, on the molecular level, there has not yet been discovered 15 a gene or group of genes that are responsible for the various forms of acne vulgaris.

Another key factor in the development of acne is hormonal. In adolescence, for example, it is thought that androgens can interact with receptors 20 on the sebaceous glands and cause stimulation of the sebaceous gland, to hypertrophy and hence form more sebaceous production of lipids and free fatty acids which distend the follicular canal. More specifically, there is evidence for increased 25 peripheral metabolic conversion of the androgen testosterone to dihydrotestosterone at the level of the skin in acne patients. It is further hypothesized that receptors on the sebaceous gland for the active androgen dihydrotestosterone can 30 exhibit various degrees of sensitivity, and that a heightened sensitivity response may be partially or entirely genetically predetermined.

Another causitive factor in acne is the presence of bacteria in the follicular canal.

35 Within the follicular canal are bacteria which are

-9-

- indigenous to the follicular lining. They are anaerobic, gram positive organisms called *Propriionibacterium acnes*. It is interesting to note that they are present in abundance in
- 5 pathologically affected sites. They are reduced during oral antimicrobial treatment, and their absence from nonhuman animal skin is striking especially since animals do not exhibit acne vulgaris.
- 10 Yet another causitive factor in acne is the inflammatory response manifested in the skin. More specifically, it is thought that *Propriionibacterium acnes* lives in symbiosis on the keratin lined follicular canal.
- 15 *Propriionibacterium acnes* ingests the sebum produced from the sebocytes of the sebaceous glands. This nascent sebum is largely lipid in composition and also contains DNA, RNA, proteins, and other cellular components that result from the
- 20 breakdown of sebocytes themselves. The *Propriionibacterium acnes* which are highly lipophilic, feed on the nascent sebum. It has been shown that *Propriionibacterium acnes* are found only in sebaceous rich areas. If the nutrients
- 25 increase due to an active and large sebaceous system, then colonization and high growth rates of *Propriionibacterium acnes* will form. It has been shown that the resident bacterial flora will produce biologically active molecules such as
- 30 histamine, extracellular enzymes, and peptides which may be responsible for the chemotaxis of the inflammatory infiltrate in acne vulgaris. Since the follicular lining in the pilosebaceous unit is intact, it has been theorized that if colonization
- 35 of *Propriionibacterium acnes* occurs in sufficient

-10-

numbers, they could produce initiating antigenic molecules that promote the initiation of inflammation. *Propriionibacterium acnes* can produce proteinases, lipase, and hyaluronate lyase

- 5 all of which may serve as the catalysts or initiators of the inflammatory infiltrate which has been shown to be composed of neutrophils and lymphocytes.

A number of treatments are presently known
10 for treating acne, some more successful than others. Some modes of treatment have been mentioned above. There are two modes of treatment, topical and systemic.

Aside from treatments mentioned above, some
15 additional systemic treatments for acne that are presently employed are: oral tetracycline; oral erythromycin; minocycline; doxycycline; oral trimethoprim-sulfamethoxazole and isotretinoin (ACUTANE TR).

20 Those that have been suggested in the past and that are no longer generally employed include: antibacterial vaccines; estrogen therapy; dietary restrictions; and vitamin therapy (e. g. oral ingestion of vitamin A).

25 Some of the topical treatments that are presently employed are: topical erythromycin, clindamycin, benzoyl peroxide, 2% sulfur, 3% resorcinol, a tetracycline derivative (meclocycline sulfosalicylate 1%), 2% salicylic acid, and tretinoin (Retin-A TR).

30 Topical treatments that have been suggested in the past and that are no longer generally employed include: x-ray treatment; electric sparks; vitamin therapy; treatment with a plant

-11-

extract as described in U. S. Patent No. 4,803,069.

- More specifically with respect to the topical use of certain specific antibiotics, a topical 5 solution, ointment, and gel containing erythromycin is used. Also used is a topical solution, gel, and lotion containing clindamycin, and a cream containing mecloxycline sulfosalicylate 1% (a tetracycline derivative).
- 10 Some of the undesirable side effects of orally administered antibiotics are abdominal cramps, black tongue, cough, diarrhea, fatigue, irritation of the mouth, loss of appetite, nausea, vomiting, fever, hearing loss, jaundice, rash, 15 rectal and vaginal itching, and superinfection.
- It is noted that erythromycin is produced by the bacterium Streptomyces erytheus and that erythromycin has a chemical structure that is substantially unique to erythromycin and its 20 derivatives. The molecular weight of erythromycin A is 733.92. The empirical formula for erythromycin A is $C_{37}H_{67}NO_{13}$ having a 60.55% carbon content, a 9.20% hydrogen content, a 1.91% nitrogen content, and a 28.34% oxygen content.
- 25 Clindamycin has a chemical structure indicated by its chemical name which is methyl 7-chloro-6,7,8-trideoxy-6-[(1-methyl-4-propyl-2-pyrrolidinyl)carbonyl]amino]-1-thio-L--threo-alpha-D-galacto-octopyranoside. The molecular 30 weight of clindamycin is 424.98. The empirical formula for clindamycin is $C_{18}H_{33}ClN_2O_5S$ having a 50.87% carbon content, a 7.83% hydrogen content, a 8.34% chlorine content, a 6.59% nitrogen content, a 18.82% oxygen content, and a 7.54% sulfur 35 content.

-12-

- Other topical treatments for acne using antibiotics are described in the following Great Britain patents: neomycin, G. B. Pat. No. 1,054,124; erythromycin, G. B. Pat. No. 1,587,428; 5 and erythromycin derivatives in conjunction with benzoyl peroxide, G. B. Pat. Nos. 2,088,717 and 2,090,135.

Still another topical treatment for acne, more specifically acne vulgaris, includes 10 preparation of a hyaluronic acid derivative which is a bridged conjugate of hyaluronic acid (which is a linear polymer of N-acetyl glucosamine and glucuronic acid units) bonded to a bridging agent (which is cyanogen bromide) which, in turn, is 15 bonded to the amino-nitrogen atom of the aminopenicillin, ampicillin. Thus, with this hyaluronic acid derivative, the amino-nitrogen of the aminopenicillin is no longer in the form of a primary amino group. This hyaluronic acid 20 derivative is disclosed in Great Britain Published Application 2,207,142.

The formulation disclosed in Great Britain Published Application 2,207,142 poses several significant problems. First, by reacting the 25 bridging agent with the primary amino-nitrogen of the aminopenicillin, the effectiveness of the aminopenicillin may be severely reduced or even eliminated. More specifically, presently, all of the aminopenicillins that are approved for 30 prescribing in the practice of medicine in the United States include an amino-nitrogen which is in the form of a primary amino group (the nitrogen atom of the primary amino group being bonded to two hydrogen atoms). Not one of these approved 35 aminopenicillins has its characteristic primary

-13-

amino group modified so that it is no longer a primary amino group.

Another significant problem posed by the hyaluronic acid derivative in disclosed in Great

- 5 Britain Published Application 2,207,142 is the fact that a very toxic bridging agent, cyanogen bromide, is disclosed. Cyanogen bromide can cause toxic effects similar to those of hydrogen cyanide. Hydrogen cyanide may cause death from
- 10 only a few minutes exposure to a concentration of approximately 300 ppm. Lesser concentrations may cause headache, vertigo, nausea, and vomiting. With these potentially serious toxic side effects of cyanogen bromide, it would be very risky to
- 15 even employ the hyaluronic derivative disclosed in Great Britain Published Application 2,207,142. More specifically, on page 5, lines 3-5 of Great Britain Published Application 2,207,142, there is a teaching that a stringy precipitate (of a
- 20 bridged hyaluronic acid/cyanogen bromide/ampicillin conjugate) is washed several times with absolute ethanol and dried in the air. Then, as disclosed on page 5, lines 16-26, the bridged hyaluronic acid/cyanogen
- 25 bromide/ampicillin conjugate, having been incorporated in a conventional medium, is applied directly to the skin to treat acne vulgaris. What is risky about using this bridged hyaluronic acid/cyanogen bromide/ampicillin conjugate is that
- 30 a quantity of unreacted cyanogen bromide remains as a residue the precipitate residue after several rinses with absolute alcohol. Then, by applying some of this bridged hyaluronic acid/cyanogen bromide/ampicillin conjugate directly to the skin
- 35 of patients, one would then be applying a residue

-14-

of cyanogen bromide directly to the skin of patients.

For the reasons stated above with respect to the bridged hyaluronic acid/cyanogen

- 5 bromide/ampicillin conjugate disclosed in Great Britain Published Application 2,207,142, it is desirable to avoid using an ampicillin in which the characteristic amino-nitrogen is not in the form of a primary amino group, and it is desirable
- 10 to avoid using a material that may contain a toxic residue such as the bridging agent cyanogen bromide.

Still other topical treatments for acne using antibacterials are described in the following U.

- 15 S. patents: an azole derivative in conjunction with benzoyl peroxide, U. S. Patent No. 4,446,145, incorporated herein by reference; and metronidazole in a special gel as described in U. S. Patent No. 4,837,378, incorporated herein by
- 20 reference.

Disclosure of Invention

Accordingly, it is an object of the invention to provide a new topical treatment for acne and acneiform dermal disorders.

- 25 Another object of the invention is to provide a new topical treatment for acne which effectively adds to the armamentarium of physicians, and in particular dermatologists, to treat heretofore resistant forms of acne for which there was no
- 30 safe, minimal side effect, and effective treatment available.

Another object of the invention is to provide a new topical treatment for acne which will avoid the undesirable side effects of the currently

-15-

available oral antibiotics for the systemic treatment of acne and acneiform dermal disorders, such as diarrhea, abdominal cramping, nausea, vomiting, drug eruptions, photosensitivity, blood dyscrasias (e. g. depression of white blood cell count and red blood cell count), drug induced hepatitis (elevation of liver functions), and teratogenicity, to name a few. Another object of the invention is to provide a topical treatment for acne which uses an aminopenicillin whose characteristic amino group is in the form of a primary amino group.

Still another object of the invention is to provide a topical treatment for acne which uses an antibiotic that does not have the risk of bearing a toxic residue of a toxic bridging agent.

These and other objects are achieved by employing the principles of the invention wherein ampicillin, amoxicillin, another aminopenicillin, or other penicillin-like derivative is mixed with a carrier and applied topically to the skin of a patient suffering from acne and other acneiform dermal disorders. In accordance with the invention described herein, the term aminopenicillin is understood to be an aminopenicillin whose characteristic amino group is in the form of a primary amino group.

Further in accordance with the invention, a cephalosporin or cephalosporin derivative is mixed with a carrier and applied topically to the skin of a patient suffering from acne and other acneiform dermal disorders. Suitable cephalosporins include cefadroxil, cefazolin, cephalexin, cephalothin, cephapirin, cephadrine, cefaclor, cefamandole, cefonicid, ceforanide,

-16-

- cefotetan (a cephamycin), cefoxitin (a cephamycin), cefuroxime, the 1-acetyloxy ethyl ester of cefuroxime (cefuroxime axetil), cefoperazone, cefotaxime, ceftazidime, ceftin,
5 ceftizoxime, ceftriaxone, and moxalactam (a 1-oxa-beta-lactam).

With the invention, a variety of treatment regimens are contemplated.

- In a first treatment regimen, topical
10 compositions of the invention are used alone to treat the acne and acneiform dermal disorders. In this respect, the topical compositions of the invention can be used as a first line treatment for acne and acneiform dermal disorders.
15 In a second treatment regimen of the invention, an orally administered antibiotic and a topical composition of the invention are used in combination. There are a number of specific courses of treatment that can be carried out in
20 this second treatment regimen. The oral antibiotic and the topical composition of the invention can be administered simultaneously from the beginning. Or, the oral administration can be begun first, and the topical administration can
25 then be begun. The oral administration can continue when the topical administration begins, or the oral administration can stop when the topical administration begins. Alternatively, the oral antibiotic and the topical composition of
30 the invention can be administered sequentially. With sequential administration, oral administration can take place first, and then topical administration can be begun.
In this respect, after a conventional regimen
35 of treating a patient for acne or acneiform dermal

-17-

disorders with an orally administered antibiotic, such as tetracycline, minocycline, doxycycline, erythromycin, wherein the patient develops resistance or no improvement, it is the teaching
5 of this invention that an antibiotic selected from the group consisting of ampicillin, amoxicillin, another aminopenicillin, penicillin-like derivatives, and cephalosporin, and derivatives and analogs thereof, is administered topically to
10 the patient.

In a third treatment regimen of the invention, conventional topical medications and topical compositions of the invention can be administered simultaneously. The conventional
15 topical medications which can be used include: benzoyl peroxide and/or topical Retin-A (TM) (tretinoin) and/or any other topical agent currently used by physicians in the treatment of acne and acneiform dermal disorders.

20 In a fourth treatment regimen of the invention, conventional oral medications, conventional topical medications, and topical compositions of the invention can be administered simultaneously. Still further in accordance
25 with the invention, a treatment for ocular rosacea, blepharitis, blepharoconjunctivitis, giant papillary conjunctivitis, meibomian gland dysfunction, and infection by Acanthamoeba organisms is provided by topically administering
30 to the eyelids and/or eyeballs a composition containing an ampicillin, amoxicillin, another aminopenicillin, other penicillin-like derivative, a cephalosporin, or derivative or analog thereof, and a suitable ophthalmological carrier selected
35 from the group consisting of an aqueous liquid, an

-18-

artificial tear solution, a water soluble gel, an ointment base, petrolatum, a nonaqueous liquid base, a mineral oil base, a blend of mineral oil and petroleum, a suspension of solid particles in 5 a liquid, and a suspension of an ion-exchange resin in water.

The ampicillin, amoxicillin, another aminopenicillin, or other penicillin-like derivative, cephalosporin, or derivative or analog 10 thereof can be administered alone or in conjunction with a nitroimidazole, such as metronidazole, disclosed in U. S. Patent No. 4,957,918, incorporated herein by reference. Furthermore, the ampicillin, amoxicillin, another 15 aminopenicillin, or other penicillin-like derivative, cephalosporin, or derivative or analog thereof can be applied subsequent to treatment with the nitroimidazole compound.

Although the inventors are not bound by any 20 theoretical explanation as to why the compositions and the methods of the invention are efficacious in treating acne and acneiform dermal disorders, presentation of certain theoretical concepts may be of value.

25 For one thing, it is felt that the efficacy of the compositions and the methods of the invention is due in part to the antibiotic qualities of the compositions employed and the fact that a portion of the topically applied 30 antibiotic is absorbed by the skin and enters the patient's bloodstream.

Another possible reason for the efficacy of the compositions and the methods of the invention is that the compositions of the invention exert an 35 anti-inflammatory effect on the cells of the

-19-

sebaceous gland unit, thereby decreasing production of neutrophils and lymphocytes which contribute to inflammation. Still another possible reason for the efficacy of the topical compositions and methods of the invention is that the topically applied antibiotic is able to kill microorganisms that cannot be killed by an orally administered antibiotic. More specifically, the topically applied antibiotic directly kills microorganisms in the sebaceous follicle that are shielded by a hydrophobic sebaceous film inside the follicle from the effects of an antibiotic in the bloodstream. The bloodstream is essentially an aqueous medium, and the hydrophobic sebaceous film blocks the antibiotic in the bloodstream, from diffusing onto the microorganisms on the other side of the sebaceous film. However, the microorganism may produce products that are fat soluble and are able to cross through the sebaceous film and thereby irritate the cells lining the sebaceous follicle. Thus, the hydrophobic sebaceous film may allow passage, in one direction, of irritants from the microorganisms to the follicle walls, but the hydrophobic sebaceous film prevents passage of antibiotic in the bloodstream from diffusing across the hydrophobic sebaceous film in the other direction to the microorganisms.

Mode for Carrying Out the Invention

It is understood herein that the term penicillin-like derivative is a compound that contains the following chemical structural components: 6-[R-carbonyl]amino]-3,3-di-methyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic

-20-

acid, where R is a reactive group substituted on the carbonyl carbon on the nitrogen atom of the 6-amino group.

Ampicillin is an aminopenicillin. Generally, 5 aminopenicillins are semisynthetic penicillin derivatives produced by acylation of 6-aminopenicillanic acid (6-APA). Aminopenicillins have a free amino group (a primary amino group) at the alpha-position on the penicillin nucleus which 10 results in enhanced activity against gram-negative bacteria compared with natural penicillins and penicillinase-resistant penicillins. It is noted that for ampicillin there is a benzylamine group on the carbonyl carbon on the nitrogen atom of the 15 6-amino group. More specifically, for ampicillin, the "R" in the formula for penicillin-like derivatives is a benzylamine group. Stated somewhat differently, for ampicillin specifically and for aminopenicillins generally, the R group 20 includes a carbon atom bonded to the carbonyl-amino carbon atom, where a primary amino group is bonded to that carbon atom bonded to the carbonyl-amino carbon atom.

Other names for ampicillin include the terms 25 ampicillin A, BRL 1341, P 50, Ay 6108, Adobacillin, Alpen, Amfipen, Ampi-Bol, Bonapicillin, Grampenil, Guicitrina, Copharcilin, Nuvapen, Synpenin, Viccillin, Ultrabion, Ampipenin, Amplisom, Amimed, Ampy-Penyl, 30 Totalciclina, Amipenix S, Amblosin, Ampicin, Amplital, Astrapen, Binotal, Britacil, Doktacillin, Marsilan, Pen-Bristol, Penbritin, Penbrock, Penicline, Pentrex, Pentrexyl, Ponecil, Polycillin, QI Damp, Toliocillin, Totacillin, and 35 Totapen.

-21-

Amoxicillin is another aminopenicillin. It is also noted that for amoxicillin there is a 4-hydroxybenzylamine group substituted on the carbonyl carbon on the nitrogen atom of the 6-amino group. More specifically, for amoxicillin the "R" in the formula for penicillin-like derivatives is a 4-hydroxybenzylamine group.

Other names for amoxicillin include the terms amoxycillin, AMPC, Amolin, Amopenixin, Amoxi, 10 Amoxipen, Anemolin, Aspenil, Bristamox, Delacillin, Efpenix, Ibiamox, Piramox, and Sumox.

It is noted that both ampicillin and amoxicillin include "R" groups comprised of benzylamine and 4-hydroxybenzylamine groups, 15 respectively. More generically, in accordance with the invention, compositions containing penicillin-like derivatives where "R" in the formula above is benzylamine and derivatives thereof. Stated somewhat differently, 20 compositions of the invention and the use thereof include ampicillin and derivatives thereof and amoxicillin and derivatives thereof. Also, the compositions of the invention and the use thereof include ampicillin, amoxicillin, or 25 pharmaceutically acceptable salts or solvates thereof.

Suitable forms of ampicillin and amoxicillin can be selected from the group consisting of ampicillin; ampicillin, monohydrate; ampicillin, 30 potassium salt; ampicillin, sesquihydrate; ampicillin, trihydrate; ampicillin, anhydrous form; ampicillin, sodium salt; ampicillin, D(-) form, L(+) form, or DL-form; other suitable ampicillin derivatives; amoxicillin; amoxicillin

-22-

trihydrate; amoxicillin hydrochloride trihydrate; amoxicillin beta-naphthalenesulfonate trihydrate; and other suitable amoxicillin derivatives.

Other suitable aminopenicillins include

5 bacampicillin and cyclacillin.

Suitable forms of other penicillin-like derivatives or analogs can be selected from the group consisting of azlocillin; acylureido penicillins related to azlocillin; carbenicillin;

- 10 carbenicillin, disodium salt; carbenicillin, indenyl; cloxacillin; dicloxacillin; dicloxacillin, sodium salt; floxacillin; isoxazolyl penicillins; hetacillin; methicillin; methicillin, sodium; mezlocillin; mezlocillin, 15 sodium salt; nafcillin oxacillin; oxacillin, sodium salt; penicillin BT; penicillin BT, procaine salt; penicillin G; penicillin G benethamine; penicillin G benzathine; penicillin G benzhydrylamine; penicillin G calcium; penicillin 20 G hydrabamine; penicillin G potassium; penicillin G procaine; penicillin N; penicillin N, barium salt; penicillin O; penicillin O, 2-chloroprocaine salt monohydrate; penicillin O, potassium salt; penicillin O, procaine salt; penicillin O, sodium 25 salt; penicillin S potassium; penicillin V; penicillin V, potassium salt; penicillin V, sodium salt; penicillin V, calcium salt; penicillin V benzathine; penicillin V hydrabamine; and phenethicillin.

- 30 More specific descriptions of some of the preferred penicillin-like derivatives or analogs are as follows.

Ampicillin has a chemical structure indicated by its chemical name which is 6-

- 35 [(aminophenylacetyl)amino]-3,3-di-methyl-7-oxo-4-

-23-

thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid. The molecular weight of ampicillin is 349.42. The empirical formula for ampicillin is $C_{16}H_{19}N_3O_4S$ having a 55.0% carbon content, a 5.48% hydrogen content, a 12.02% nitrogen content, a 18.32% oxygen content, and a 9.18% sulfur content.

Amoxicillin has a chemical structure indicated by its chemical name which is 6-[[amino(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid. The molecular weight of amoxicillin is 365.41. The empirical formula for amoxicillin is $C_{16}H_{19}N_3O_5S$ having a 52.59% carbon content, a 5.24% hydrogen content, a 11.50% nitrogen content, a 21.89% oxygen content, and a 8.77% sulfur content.

It is understood herein that the term cephalosporin derivative is a compound that contains the following chemical structural components: 3-[(acetyloxy)methyl]-7-[(R)-amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, where R is a reactive group substituted on the nitrogen of the 7-amino group.

It is noted that for cephalosporin C there is a 5-amino-5-carboxy-1-oxopentyl group on the nitrogen of the 7-amino group. More specifically, for cephalosporin C, the "R" in the formula for cephalosporin derivatives is a 5-amino-5-carboxy-1-oxopentyl group.

It is noted that for cephalothin there is a 2-thienyl5-amino-5-carboxy-1-oxopentyl group on the nitrogen of the 7-amino group. More specifically, for cephalothin, the "R" in the formula for cephalosporin derivatives is a 5-amino-5-carboxy-1-oxopentyl group.

-24-

Specific suitable cephalosporin derivatives are as follows: cephalosporin C; cephalosporin C, sodium salt, dihydrate; cephalothin; cephalothin, sodium salt (also known as Averon-1, Cefalotin, 5 Cephation, Ceporacin, Cepovenin, Chephalotin, Coaxin, Keflin, Lospoven, Microtin, Synclotin, and Toricelocin); cephapirin sodium; cefadroxil; cefazolin; cephalexin; cephalothin; cephapirin; cephradine; cefaclor; cefamandole; cefonicid; 10 ceforanide; cefotetan (a cephemycin); cefoxitin (a cephemycin); ceftin; cefuroxime; the 1-acetyloxy ethyl ester of cefuroxime (cefuroxime axetil); cefoperazone; cefotaxime; ceftazidime; ceftizoxime; ceftriaxone; and moxalactam (a 1-oxa-15 beta-lactam).

In addition, analogs of cephalosporin are also suitable for topical treatment of acne. These cephalosporin analogs include: cephalosporin P.; cephemycins; cepharanthine; and 20 cephradine.

Suitable carriers for the form of ampicillin, amoxicillin, or other penicillin-like derivative or cephalosporin or cephalosporin derivative or cephalosporin analog can be selected from the 25 group consisting of: a petrolatum vehicle; a water soluble gel; a mineral oil base; a blend of mineral oil and petrolatum; a suspension of an ion-exchange resin, e. g. Amberlite, in water; and other suitable pharmaceutical carriers, well known 30 in the art.

By selection of a suitable vehicle, the ampicillin, amoxicillin, cephalosporin etc. can be administered topically as a solution, a gel, a lotion, a cream, or an ointment.

-25-

In addition to the form of ampicillin, amoxicillin, another aminopenicillin, or other penicillin-like derivative or cephalosporin or cephalosporin derivative or cephalosporin analog

- 5 that is employed as an active ingredient, another active ingredient, such as benzoyl peroxide can be used.

For a topical formulation, in addition to the form of ampicillin, amoxicillin, another

- 10 aminopenicillin, or other penicillin-like derivative, or cephalosporin or cephalosporin derivative or cephalosporin analog, the carrier, and possibly another active ingredient, the formulation can also include an agent which
15 enhances penetration of an active ingredient through the skin. Exemplary agents which increase skin penetration are disclosed in the following U. S. patents all of which are incorporated herein by reference: U. S. Patent No. 4,537,776 (a binary
20 combination of N-(hydroxyethyl)pyrrolidone and a cell-envelope disordering compound); U. S. Patent No. 4,130,667 (using a sugar ester in combination with a sulfoxide or phosphine oxide); and U. S. Patent No. 3,952,099 (using sucrose monooleate,
25 decyl methyl sulfoxide, and alcohol).

Other exemplary materials that increase skin penetration are surfactants or wetting agents which include the following: polyoxyethylene sorbitan mono-oleate (Polysorbate 80); sorbitan

- 30 mono-oleate (Span 80); p-isooctyl polyoxyethylene-phenol polymer (Triton WR-1330); polyoxyethylene sorbitan tri-oleate (Tween 85); dioctyl sodium sulphosuccinate; and sodium sarcosinate (Sarcosyl NL-97); and other pharmaceutically acceptable
35 surfactants.

-26-

Although there is not a complete understanding of the detailed theoretical mechanism upon which the efficacy of the topical dermatological compositions of the present invention which contain ampicillin, amoxicillin, another aminopenicillin, and other penicillin-like derivatives are founded, this lack of theoretical understanding in no way diminishes the benefits derived from employing the compositions and methods of the invention and in no way detracts from the utility of the invention as described herein.

Nevertheless, although not proven conclusively, it is felt that the topical use of ampicillin, amoxicillin, another aminopenicillin, and other penicillin-like derivatives or cephalosporin or cephalosporin derivative or cephalosporin analog of the invention help diminish the presence of Propriionibacterium acnes, and therefore diminish the effects on acne caused by the presence of Propriionibacterium acnes.

Furthermore, although not proven conclusively, it is felt that the topical use of ampicillin, amoxicillin, another aminopenicillin, and other penicillin-like derivatives or cephalosporin or cephalosporin derivative or cephalosporin analog of the invention serves to inhibit the skin's inflammatory response. More specifically, it is felt that by using the principles of the invention, there is a decrease in chemotaxis of lymphocytes and neutrophils toward the pilosebaceous unit where inflammation and follicular plugging, and sebaceous fluid are accumulating. It may be that the major effect of topical ampicillin and amoxicillin is this anti-

-27-

chemotactic effect of neutrophils and lymphocytes.

A variety of suitable compositions of the invention are presented below in Examples 1-82.

Example 1

- 5 A topical dermatological composition containing ampicillin is obtained as follows. Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
10	Ethyl alcohol	42.0
	Laureth-4	0.5
	Isopropyl alcohol	6.0
	Ampicillin	2.0
	Purified water	49.5

- 15 Citric acid can be used to adjust the pH to a desired level.

The composition in Example 1 contains approximately 2% ampicillin.

- Other suitable compositions can be made in accordance with Example 1 which include ampicillin in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

Example 2

- 25 A topical dermatological composition containing amoxicillin is obtained as follows. Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
	Ethyl alcohol	42.0
30	Laureth-4	0.5
	Isopropyl alcohol	6.0
	Amoxicillin	2.0
	Purified water	49.5

-28-

Citric acid can be used to adjust the pH to a desired level.

The composition in Example 2 contains approximately 2% amoxicillin.

- 5 Other suitable compositions can be made in accordance with Example 2 which include amoxicillin in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

Example 3

- 10 A topical dermatological composition containing ampicillin is obtained as follows. Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
15	Ethyl alcohol	71.2
	Propylene glycol	26.8
	Ampicillin	2.0

The composition in Example 3 contains approximately 2% ampicillin.

20 Example 4

- A topical dermatological composition containing amoxicillin is obtained as follows. Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
25	Ethyl alcohol	71.2
	Propylene glycol	26.8
	Amoxicillin	2.0

The composition in Example 4 contains approximately 2% amoxicillin.

Other suitable compositions can be made in accordance with Example 4 which include

-29-

amoxicillin in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

Other topical dermatological compositions are presented below.

5 Example 5

A formulation employing a water soluble gel as a carrier is obtained as follows. More details of the gel carrier are described in U. S. Patent No. 4,837,378, incorporated herein by reference.

- 10 A 30 kilogram batch of a composition of the present invention containing ampicillin (as 0.75% by weight) is prepared as follows. 180 grams of Carbopol 940 (TM) (0.6% by weight of the final weight of the composition) was dissolved in 16.5
15 liters of distilled water containing 15 grams of ethylenediaminetetraacetic acid (EDTA) disodium dihydrate. Sufficient amount of 10 wt% sodium hydroxide (NaOH) solution is added to bring the pH value to about 5. This aqueous polymer solution
20 is called "Part A". "Part B" is prepared by mixing 900 grams of propylene glycol (3% by weight of the final weight of the composition), 24 grams of methyl paraben (0.08% by weight of the final weight of the composition), and 6.0 grams of
25 propyl paraben (0.02% by weight of the final weight of the composition). The mixture is added to 225 grams of ampicillin dispersed in 11.4 liters of distilled water maintained at 50 degrees Centrigrade. Parts A and B are then mixed
30 thoroughly and gelling of the composition results. A cold aqueous solution of NaOH is then used to adjust the final pH value to approximately 5.25. Distilled water is then added to give the desired

-30-

30 kilogram final weight. The NaOH and water are thoroughly mixed into a viscous gel.

Other suitable compositions can be made in accordance with Example 5 which include ampicillin

- 5 in the following percentages: 0.5%, 1%, 2%, 3%,
4%, 5%, and 10%.

Example 6

A formulation employing a water soluble gel as a carrier is obtained as follows. More details 10 of the gel carrier are described in U. S. Patent No. 4,837,378, incorporated herein by reference.

A 30 kilogram batch of a composition of the present invention containing amoxicillin (as 0.75% by weight) is prepared as follows. 180 grams of 15 Carbopol 940 (TM) (0.6% by weight of the final weight of the composition) was dissolved in 16.5 liters of distilled water containing 15 grams of ethylenediaminetetraacetic acid (EDTA) disodium dihydrate. Sufficient amount of 10 wt% sodium 20 hydroxide (NaOH) solution is added to bring the pH value to about 5. This aqueous polymer solution is called "Part A". "Part B" is prepared by mixing 900 grams of propylene glycol (3% by weight of the final weight of the composition), 24 grams 25 of methyl paraben (0.08% by weight of the final weight of the composition), and 6.0 grams of propyl paraben (0.02% by weight of the final weight of the composition). The mixture is added to 225 grams of amoxicillin dispersed in 11.4 30 liters of distilled water maintained at 50 degrees Centrigrade. Parts A and B are then mixed thoroughly and gelling of the composition results. A cold aqueous solution of NaOH is then used to adjust the final pH value to approximately 5.25.

-31-

Distilled water is then added to give the desired 30 kilogram final weight. The NaOH and water are thoroughly mixed into a viscous gel.

Other suitable compositions can be made in
5 accordance with Example 6 which include amoxicillin in the following percentages: 0.5%, 1%, 2%, 3%, 4%, 5%, and 10%.

Example 7

Another topical dermatological gel is
10 obtained by mixing the following ingredients in suitable amounts: allantoin, carbomer 934P, methylparaben, polyethylene glycol 400, propylene glycol, sodium hydroxide, purified water and ampicillin.

15 Example 8

Another topical dermatological gel is obtained by mixing the following ingredients in suitable amounts: allantoin, carbomer 934P, methylparaben, polyethylene glycol 400, propylene 20 glycol, sodium hydroxide, purified water and amoxicillin.

Example 9

A dermatological lotion is obtained by mixing the following ingredients in the amounts

25 specified:

<u>Ingredient</u>	<u>Weight Per Cent</u>
Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Isopropyl myristate	5
30 Butylated hydroxyanisole	0.10
Polyoxyl 40 stearate	0.25
Water, deionized or distilled	71.8

-32-

Propylene glycol	3
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
Ampicillin	2

- 5 Other suitable compositions can be made in accordance with Example 9 which include ampicillin in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

Example 10

- 10 A dermatological lotion is obtained by mixing the following ingredients in the amounts specified:

	<u>Ingredient</u>	<u>Weight Per Cent</u>
	Ethoxylated cetyl-stearyl alcohol	7
15	Cetyl alcohol	0.75
	Isopropyl myristate	5
	Butylated hydroxyanisole	0.10
	Polyoxy 40 stearate	0.25
	Water, deionized or distilled	71.8
20	Propylene glycol	3
	Acetone	10
	Dioctyl sodium sulphosuccinate	0.1
	Amoxicillin	2

- Other suitable compositions can be made in accordance with Example 10 which include amoxicillin in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

Example 11

A powdery composition is obtained as follows.

- 30 Mix the following ingredients in the amounts specified.

<u>Ingredient</u>	<u>Weight Per Cent</u>
Benzoyl peroxide (micronized)	1 to 35

-33-

Calcium phosphate	63 to 98.5
Ampicillin	0.5 to 5

Example 12

A liquid composition is obtained as follows.

- 5 Mix the following ingredients in the amounts specified.

<u>Ingredient</u>	<u>Weight Per Cent</u>
Ampicillin	0.5 to 5
Benzoyl peroxide (micronized)	1 to 30
10 Ethanol	The Balance to 100%

Example 13

A topical dermatological composition containing ampicillin is obtained as follows.

Mix the following ingredients in the amounts

- 15 specified.

<u>Ingredient</u>	<u>Weight Per Cent</u>
Ethyl alcohol	44.0
Laureth-4	0.5
Isopropyl alcohol	6.0
20 Ampicillin	2.0
Purified water	49.5

Citric acid can be used to adjust the pH to a desired level.

- The composition in Example 13 contains
25 approximately 2% ampicillin.

Other suitable compositions can be made in accordance with Example 13 which include ampicillin in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

-34-

Example 14

A lotion composition is obtained as follows.

Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
5	Ethoxylated cetyl-stearyl alcohol	7
	Cetyl alcohol	0.75
	Isopropyl myristate	5
	Butylated hydroxyanisole	0.10
10	Polyoxyl 40 stearate	0.25
	Water, deionized or distilled	66.8
	Propylene glycol	3
	Benzoyl peroxide (micronized)	5
	Acetone	10
15	Dioctyl sodium sulphosuccinate	0.1
	Ampicillin	2

Other suitable compositions can be made in accordance with Example 14 which include ampicillin in the following percentages: 0.5%,

20 1%, 3%, 4%, 5%, and 10%.

Example 15

A cream composition is obtained as follows.

Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
25	Ethoxylated cetyl-stearyl alcohol	15
	Cetyl alcohol	1.25
	Isopropyl myristate	5
	Butylated hydroxyanisole	0.10
30	Polyoxyl 40 stearate	0.25
	Water, deionized or distilled	57.30
	Propylene glycol	3
	Benzoyl peroxide (micronized)	5
	Acetone	10

-35-

Dioctyl sodium sulphosuccinate	0.1
Ampicillin	3

Other suitable compositions can be made in accordance with Example 15 which include

- 5 ampicillin in the following percentages: 0.5%, 1%, 2%, 4%, 5%, and 10%.

Example 16

A gel composition is obtained as follows.

Mix the following ingredients in the amounts
10 specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
	Water, deionized or distilled	51.65
	Butylated hydroxyanisole	0.10
	Benzoyl peroxide (micronized)	5
15	Dioctyl sodium sulphosuccinate	1
	Colloidal Bentonite	2.5
	Carboxy vinyl polymer (acid form)	1
	Ethyl alcohol	35
	Diisopropanolamine	0.75
20	Ampicillin	3

Other suitable compositions can be made in accordance with Example 16 which include ampicillin in the following percentages: 0.5%, 1%, 2%, 4%, 5%, and 10%.

25 Example 17

A suspension composition is obtained as follows. Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
30	Water, deionized or distilled	54.97
	Butylated hydroxyanisole	0.10
	Benzoyl peroxide (micronized)	5
	Dioctyl sodium sulphosuccinate	1

-36-

Colloidal Bentonite	1.5
Carboxy vinyl polymer (acid form)	0.25
Ethyl alcohol	35
Diisopropanolamine	0.18
5 Ampicillin	2

Other suitable compositions can be made in accordance with Example 17 which include ampicillin in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

10 Example 18

A powdery composition is obtained as follows. Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
15	Benzoyl peroxide (micronized)	1 to 35
	Calcium phosphate	63 to 98.5
	Amoxicillin	0.5 to 5

Example 19

A liquid composition is obtained as follows. Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
	Amoxicillin	0.5 to 5
	Benzoyl peroxide (micronized)	1 to 30
25	Ethanol	The Balance to 100%

Example 20

A lotion composition is obtained as follows. Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
	Ethoxylated cetyl-stearyl alcohol	7
	Cetyl alcohol	0.75

-37-

	Isopropyl myristate	5
	Butylated hydroxyanisole	0.10
	Polyoxyl 40 stearate	0.25
	Water, deionized or distilled	66.8
5	Propylene glycol	3
	Benzoyl peroxide (micronized)	5
	Acetone	10
	Dioctyl sodium sulphosuccinate	0.1
	Amoxicillin	2
10	Other suitable compositions can be made in accordance with Example 20 which include amoxicillin in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.	

Example 21

- 15** A cream composition is obtained as follows. Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
	Ethoxylated cetyl-stearyl alcohol	15
20	Cetyl alcohol	1.25
	Isopropyl myristate	5
	Butylated hydroxyanisole	0.10
	Polyoxyl 40 stearate	0.25
	Water, deionized or distilled	57.30
25	Propylene glycol	3
	Benzoyl peroxide (micronized)	5
	Acetone	10
	Dioctyl sodium sulphosuccinate	0.1
	Amoxicillin	3
30	Other suitable compositions can be made in accordance with Example 21 which include amoxicillin in the following percentages: 0.5%, 1%, 2%, 4%, 5%, and 10%.	

-38-

Example 22

A gel composition is obtained as follows.

Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
5	Water, deionized or distilled	51.65
	Butylated hydroxyanisole	0.10
	Benzoyl peroxide (micronized)	5
	Dioctyl sodium sulphosuccinate	1
10	Colloidal Bentonite	2.5
	Carboxy vinyl polymer (acid form)	1
	Ethyl alcohol	35
	Diisopropanolamine	0.75
	Amoxicillin	3
15	Other suitable compositions can be made in accordance with Example 22 which include amoxicillin in the following percentages: 0.5%, 1%, 2%, 4%, 5%, and 10%.	

Example 23

20 A suspension composition is obtained as follows. Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
20	Water, deionized or distilled	54.97
25	Butylated hydroxyanisole	0.10
	Benzoyl peroxide (micronized)	5
	Dioctyl sodium sulphosuccinate	1
	Colloidal Bentonite	1.5
	Carboxy vinyl polymer (acid form)	0.25
30	Ethyl alcohol	35
	Diisopropanolamine	0.18
	Amoxicillin	2

Other suitable compositions can be made in accordance with Example 23 which include

-39-

ampicillin in the following percentages: 0.5%,
1%, 3%, 4%, 5%, and 10%.

Example 24

5 An oil-in-water emulsion containing
ampicillin in ointment form is obtained as
follows.

Part A is comprised of a 3.33% aqueous
solution of ampicillin.

Part B is an ointment base comprised of:

10	<u>Ingredient</u>	<u>Weight Per Cent</u>
	viscid paraffin	35
	white vaseline	35
	cetylstearyl alcohol	30

A mixture is obtained as follows. Mix 60 ml.
15 of Part A is mixed with 40 ml. of Part B to
provide an oil-in-water emulsion in ointment form
containing approximately 2% ampicillin.

Other suitable compositions can be made in
accordance with Example 24 which include
20 ampicillin in the following percentages: 0.5%,
1%, 3%, 4%, 5%, and 10%.

Example 25

A mineral-oil-based ampicillin ointment is
obtained as follows.

25 Part A is comprised of a 6.66% aqueous
solution of ampicillin.

Part B is an ointment base comprised of:

	<u>Ingredient</u>	<u>Parts</u>
	glycerin	5
30	isopropyl alcohol, 96%	5
	mineral oil	60

A mixture is obtained as follows. Mix 30 ml.
of Part A with 70 ml. of Part B to provide a

-40-

mineral-oil-based ointment containing approximately 2% ampicillin.

Other suitable compositions can be made in accordance with Example 25 which include

- 5 ampicillin in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

From the volumes in this Example, it is easy to convert to approximate weight percents. To make the conversion, the known densities of water,

- 10 isopropyl alcohol, glycerin, and mineral oil are employed. The known density of water is approximately 1 g/ml. The known density of water is approximately 0.78 g/ml. The known density of glycerin is approximately 1.25 g/ml. The known
15 density of mineral oil is approximately 0.85 g/ml.

The weight of the 30 ml. of part A is approximately 30 grams, in view of the fact that part A is predominantly water. By taking 30 ml. of part A, approximately 2 grams of antibiotic (30
20 g. X 6.66%) and approximately 28 grams of water (30 g. X 93.34%) are obtained.

By taking 70 ml. of part B, approximately 3.9 grams of isopropyl alcohol (5 ml. X 0.78g/ml.), approximately 6.25 grams of glycerin (5 ml. X
25 1.25g/ml.), and approximately 51 grams of mineral oil (60 ml. X 0.85g/ml.) are obtained. The weight of 70 ml. of part B is approximately 61.15 grams (3.9 g. + 6.25 g. + 51 g.).

Therefore, the total weight of parts A and B
30 combined is approximately 91.15 grams (30 g. + 61.15 g.).

In the combination of parts A and B, the weight percents of the individual carrier components are as approximately as follows:

- 35 water, 31%; isopropyl alcohol, 4.3%; glycerin,

-41-

6.86%; and mineral oil, 55.95%. It is noted that the combined weight percentages of the water-miscible alcohols is approximately 11.2% (4.3% + 6.86%). It is also noted that the combined weight percentages of the water and water-miscible alcohols is approximately 42.2% (31% + 11.2%).

Example 26

A topical dermatological composition containing cephalosporin C is obtained as follows.

- 10 Mix the following ingredients in the amounts specified.

<u>Ingredient</u>	<u>Weight Per Cent</u>
Ethyl alcohol	44.0
Laureth-4	0.5
15 Isopropyl alcohol	6.0
Cephalosporin C	1.0
Purified water	balance

Citric acid can be used to adjust the pH to a desired level.

- 20 The composition in Example 26 contains approximately 1% Cephalosporin C.

Other suitable compositions can be made in accordance with Example 26 which include Cephalosporin C in the following percentages:

- 25 0.5%, 2%, 3%, 4%, 5%, and 10%.

Example 27

A topical dermatological composition containing cephalosporin C is obtained as follows.

Mix the following ingredients in the amounts

- 30 specified.

-42-

<u>Ingredient</u>	<u>Weight Per Cent</u>
Ethyl alcohol	71.2
Propylene glycol	26.8
Cephalosporin C	2.0

5 The composition in Example 27 contains approximately 2% cephalosporin C.

Other topical dermatological compositions are presented below.

Example 28

10 A formulation employing a water soluble gel as a carrier is obtained as follows. More details of the gel carrier are described in U. S. Patent No. 4,837,378, incorporated herein by reference.

A 30 kilogram batch of a composition of the present invention containing cephalosporin C (as 0.75% by weight) is prepared as follows. 180 grams of Carbopol 940 (TM) (0.6% by weight of the final weight of the composition) was dissolved in 16.5 liters of distilled water containing 15 grams of ethylenediaminetetraacetic acid (EDTA) disodium dihydrate. Sufficient amount of 10 wt% sodium hydroxide (NaOH) solution is added to bring the pH value to about 5. This aqueous polymer solution is called "Part A". "Part B" is prepared by mixing 900 grams of propylene glycol (3% by weight of the final weight of the composition), 24 grams of methyl paraben (0.08% by weight of the final weight of the composition), and 6.0 grams of propyl paraben (0.02% by weight of the final weight of the composition). The mixture is added to 225 grams of cephalosporin C dispersed in 11.4 liters of distilled water maintained at 50 degrees Centigrade. Parts A and B are then mixed thoroughly and gelling of the composition results.

-43-

A cold aqueous solution of NaOH is then used to adjust the final pH value to approximately 5.25. Distilled water is then added to give the desired 30 kilogram final weight. The NaOH and water are 5 thoroughly mixed into a viscous gel.

Other suitable compositions can be made in accordance with Example 28 which include cephalosporin C in the following percentages: 0.5%, 1%, 2%, 3%, 4%, 5%, and 10%.

10 Example 29

Another topical dermatological gel is obtained by mixing the following ingredients in suitable amounts: allantoin, carbomer 934P, methylparaben, polyethylene glycol 400, propylene 15 glycol, sodium hydroxide, purified water and cephalosporin C.

Example 30

A dermatological lotion containing ampicillin is obtained by mixing the following ingredients in 20 the amounts specified. The ingredients in Container A is blended with the ingredients in Container B.

In Container A:

	<u>Ingredient</u>	<u>Weight Per Cent of ingredient in overall lotion</u>
25	Ethoxylated cetyl-stearyl alcohol	7.00
	Cetyl alcohol	0.75
	Isopropyl myristate	5.00
30	Butylated hydroxyanisole	0.10
	Polyoxyl 40 stearate	0.25
	Water, deionized or distilled	70.80
	Propylene glycol	3.00
	Acetone	7.00

-44-

Dioctyl sodium sulfosuccinate	0.10
-------------------------------	------

In Container B:

	<u>Ingredient</u>	<u>Weight Per Cent of ingredient in overall lotion</u>
5		
	Acetone	3.00
	ampicillin	3.00

Citric acid can be used to adjust the pH to a desired level.

10 To obtain the lotion composition in Example 30, the composition in Container A is prepared. This composition in Container A is stable for long periods of time.

15 Container B can contain only ampicillin for a long period of time. Just prior to forming the complete lotion composition, 3 grams of acetone are added to Container B to dissolve the ampicillin. Then, the contents of Container A and Container B are combined to form the complete lotion composition of the invention.

The composition in Example 30 contains approximately 3% ampicillin.

Other suitable compositions can be made in accordance with Example 30 which include 25 ampicillin in the following percentages: 0.5%, 1%, 2%, 4%, 5%, and 10%.

Example 31

A powdery composition is obtained as follows. Mix the following ingredients in the amounts 30 specified.

<u>Ingredient</u>	<u>Weight Per Cent</u>
Benzoyl peroxide (micronized)	1 to 35
Calcium phosphate	63 to 98.5

-45-

Cephalosporin C 0.5 to 5

Example 32

A liquid composition is obtained as follows.

Mix the following ingredients in the amounts
5 specified.

<u>Ingredient</u>	<u>Weight Per Cent</u>
Cephalosporin C	0.5 to 5
Benzoyl peroxide (micronized)	1 to 30
Ethanol	The Balance to 100%

10 Example 33

A lotion composition is obtained as follows.

Mix the following ingredients in the amounts
specified.

<u>Ingredient</u>	<u>Weight Per Cent</u>
15 Ethoxylated cetyl-stearyl alcohol	7
Cetyl alcohol	0.75
Isopropyl myristate	5
Butylated hydroxyanisole	0.10
Polyoxyl 40 stearate	0.25
20 Water, deionized or distilled	66.8
Propylene glycol	3
Benzoyl peroxide (micronized)	5
Acetone	10
Dioctyl sodium sulphosuccinate	0.1
25 Cephalosporin C	2

Other suitable compositions can be made in
accordance with Example 33 which include
cephalosporin C in the following percentages:
0.5%, 1%, 3%, 4%, 5%, and 10%.

30 Example 34

-46-

A cream composition is obtained as follows.

Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
5	Ethoxylated cetyl-stearyl alcohol	15
	Cetyl alcohol	1.25
	Isopropyl myristate	5
	Butylated hydroxyanisole	0.10
	Polyoxyl 40 stearate	0.25
10	Water, deionized or distilled	57.30
	Propylene glycol	3
	Benzoyl peroxide (micronized)	5
	Acetone	10
	Dioctyl sodium sulphosuccinate	0.1
15	Cephalosporin C	3

Other suitable compositions can be made in accordance with Example 34 which include cephalosporin C in the following percentages: 0.5%, 1%, 2%, 4%, 5%, and 10%.

20 Example 35

A gel composition is obtained as follows.

Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
25	Water, deionized or distilled	51.65
	Butylated hydroxyanisole	0.10
	Benzoyl peroxide (micronized)	5
	Dioctyl sodium sulphosuccinate	1
	Colloidal Bentonite	2.5
30	Carboxy vinyl polymer (acid form)	1
	Ethyl alcohol	35
	Diisopropanolamine	0.75
	Cephalosporin C	3

-47-

Other suitable compositions can be made in accordance with Example 35 which include cephalosporin C in the following percentages: 0.5%, 1%, 2%, 4%, 5%, and 10%.

5 Example 36

A suspension composition is obtained as follows. Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
10	Water, deionized or distilled	54.97
	Butylated hydroxyanisole	0.10
	Benzoyl peroxide (micronized)	5
	Dioctyl sodium sulphosuccinate	1
	Colloidal Bentonite	1.5
15	Carboxy vinyl polymer (acid form)	0.25
	Ethyl alcohol	35
	Diisopropanolamine	0.18
	Cephalosporin C	2

Other suitable compositions can be made in accordance with Example 36 which include cephalosporin C in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

Example 37

A topical dermatological composition containing amoxicillin is obtained as follows. Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
	Ethyl alcohol	44.0
30	Laureth-4	0.5
	Isopropyl alcohol	6.0
	Amoxicillin	2.0
	Purified water	49,5

-48-

Citric acid can be used to adjust the pH to a desired level.

The composition in Example 37 contains approximately 2% amoxicillin.

5 Other suitable compositions can be made in accordance with Example 37 which include amoxicillin in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

Example 38

10 A topical dermatological composition containing ceftin is obtained as follows. Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
15	Ethyl alcohol	44.0
	Laureth-4	0.5
	Isopropyl alcohol	6.0
	Ceftin	1.0
	Purified water	balance

20 Citric acid can be used to adjust the pH to a desired level.

The composition in Example 38 contains approximately 1% Ceftin.

Other suitable compositions can be made in
25 accordance with Example 38 which include Ceftin in the following percentages: 0.5%, 2%, 3%, 4%, 5%, and 10%. Example 37

Example 39

A dermatological lotion is obtained by mixing
30 the following ingredients in suitable amounts: ampicillin (approximately 1% by weight); and a carrier which includes isopropyl alcohol (approximately 80% by weight), purified water

-49-

(approximately 9% by weight), and propylene glycol (approximately 10% by weight).

Example 40

A dermatological lotion is obtained by mixing
5 the following ingredients in suitable amounts:
amoxicillin (approximately 1% by weight); and a
carrier which includes isopropyl alcohol
(approximately 80% by weight), purified water
(approximately 9% by weight), and propylene glycol
10 (approximately 10% by weight).

Example 41

A dermatological lotion is obtained by mixing
the following ingredients in suitable amounts:
cephalosporin C (approximately 1% by weight); and
15 a carrier which includes isopropyl alcohol
(approximately 80% by weight), purified water
(approximately 9% by weight), and propylene glycol
(approximately 10% by weight).

Example 42

20 A topical dermatological composition
containing cephalexin is obtained as follows.
Mix the following ingredients in the amounts
specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
25	Ethyl alcohol	42.0
	Laureth-4	0.5
	Isopropyl alcohol	6.0
	Cephalexin	1.0
	Purified water	balance
30	Citric acid can be used to adjust the pH to a desired level.	

-50-

The composition in Example 42 contains approximately 1% Cephalexin.

Other suitable compositions can be made in accordance with Example 42 which include

- 5 Cephalexin in the following percentages: 0.5%, 2%, 3%, 4%, 5%, and 10%.

Example 43

A topical dermatological composition containing cephalexin is obtained as follows.

- 10 Mix the following ingredients in the amounts specified.

<u>Ingredient</u>	<u>Weight Per Cent</u>
Ethyl alcohol	48.0
Laureth-4	0.5
15 Isopropyl alcohol	4.0
Propylene glycol	10.0
Cephalexin	1.0
Purified water	balance

- Citric acid can be used to adjust the pH to a
20 desired level.

The composition in Example 43 contains approximately 1% Cephalexin.

Other suitable compositions can be made in accordance with Example 43 which include

- 25 Cephalexin in the following percentages: 0.5%, 2%, 3%, 4%, 5%, and 10%.

Example 44

A topical dermatological composition containing Cephalexin is obtained as follows.

- 30 Mix the following ingredients in the amounts specified.

<u>Ingredient</u>	<u>Weight Per Cent</u>
Ethyl alcohol	44.0

-51-

Laureth-4	0.5
Isopropyl alcohol	6.0
Cephalexin	1.0
Purified water	balance

- 5 Citric acid can be used to adjust the pH to a desired level.

 The composition in Example 44 contains approximately 1% Cephalexin.

- Other suitable compositions can be made in
 10 accordance with Example 44 which include Cephalexin in the following percentages: 0.5%, 2%, 3%, 4%, 5%, and 10%.

Example 45

- A topical dermatological composition
 15 containing cephalexin is obtained as follows.
 Mix the following ingredients in the amounts specified.

<u>Ingredient</u>	<u>Weight Per Cent</u>
Ethyl alcohol	48.0
20 Laureth-4	0.5
Isopropyl alcohol	4.0
Propylene glycol	10.0
Cephalexin	1.0
Purified water	balance

- 25 Citric acid can be used to adjust the pH to a desired level.

 The composition in Example 45 contains approximately 1% Cephalexin.

- Other suitable compositions can be made in
 30 accordance with Example 45 which include Cephalexin in the following percentages: 0.5%, 2%, 3%, 4%, 5%, and 10%.

-52-

Example 46

A topical dermatological composition containing cefaclor is obtained as follows.

Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
5	Ethyl alcohol	44.0
	Laureth-4	0.5
	Isopropyl alcohol	6.0
10	Cefaclor	2.0
	Purified water	balance

Citric acid can be used to adjust the pH to a desired level.

The composition in Example 46 contains approximately 2% Cefaclor.

Other suitable compositions can be made in accordance with Example 46 which include Cefaclor in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

20 Example 47

A topical dermatological composition containing cefaclor is obtained as follows.

Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
25	Ethyl alcohol	48.0
	Laureth-4	0.5
	Isopropyl alcohol	4.0
	Propylene glycol	10.0
30	Cefaclor	1.0
	Purified water	balance

Citric acid can be used to adjust the pH to a desired level.

-53-

The composition in Example 47 contains approximately 1% Cefaclor.

Other suitable compositions can be made in accordance with Example 47 which include Cefaclor

- 5 in the following percentages: 0.5%, 2%, 3%, 4%, 5%, and 10%.

Example 48

A topical dermatological composition containing cefuroxime is obtained as follows.

- 10 Mix the following ingredients in the amounts specified.

<u>Ingredient</u>	<u>Weight Per Cent</u>
Ethyl alcohol	44.0
Laureth-4	0.5
15 Isopropyl alcohol	6.0
Cefuroxime	1.0
Purified water	balance

Citric acid can be used to adjust the pH to a desired level.

- 20 The composition in Example 48 contains approximately 1% Cefuroxime.

Other suitable compositions can be made in accordance with Example 48 which include Cefuroxime in the following percentages: 0.5%, 2%, 3%, 4%, 5%, and 10%.

- 25 2%, 3%, 4%, 5%, and 10%.

Example 49

A topical dermatological composition containing cefuroxime is obtained as follows.

Mix the following ingredients in the amounts

- 30 specified.

<u>Ingredient</u>	<u>Weight Per Cent</u>
Ethyl alcohol	48.0
Laureth-4	0.5

-54-

- | | | |
|----|--|---------|
| | Isopropyl alcohol | 4.0 |
| | Propylene glycol | 10.0 |
| | Cefuroxime | 1.0 |
| | Purified water | balance |
| 5 | Citric acid can be used to adjust the pH to a desired level. | |
| | The composition in Example 49 contains approximately 1% Cefuroxime. | |
| | Other suitable compositions can be made in | |
| 10 | accordance with Example 49 which include Cefuroxime in the following percentages: 0.5%, 2%, 3%, 4%, 5%, and 10%. | |

Example 50

A topical dermatological composition containing cefuroxime axetil is obtained as follows. It is noted that cefuroxime axetil is the 1-acetyloxy ethyl ester of cefuroxime. Mix the following ingredients in the amounts specified.

20	<u>Ingredient</u>	<u>Weight Per Cent</u>
	Ethyl alcohol	44.0
	Laureth-4	0.5
	Isopropyl alcohol	6.0
	Cefuroxime axetil	1.0
25	Purified water	balance

Citric acid can be used to adjust the pH to a desired level.

The composition in Example 50 contains approximately 1% Cefuroxime axetil.

30 Other suitable compositions can be made in accordance with Example 50 which include Cefuroxime axetil in the following percentages: 0.5%, 2%, 3%, 4%, 5%, and 10%.

-55-

Example 51

A topical dermatological composition containing cefuroxime axetil is obtained as follows.

- 5 Mix the following ingredients in the amounts specified.

<u>Ingredient</u>	<u>Weight Per Cent</u>
Ethyl alcohol	48.0
Laureth-4	0.5
10 Isopropyl alcohol	4.0
Propylene glycol	10.0
Cefuroxime axetil	1.0
Purified water	balance

- Citric acid can be used to adjust the pH to a
15 desired level.

The composition in Example 51 contains approximately 1% Cefuroxime axetil.

Other suitable compositions can be made in accordance with Example 51 which include

- 20 Cefuroxime axetil in the following percentages:
0.5%, 2%, 3%, 4%, 5%, and 10%.

Example 52

A topical dermatological composition containing cefoperazone is obtained as follows.

- 25 Mix the following ingredients in the amounts specified.

<u>Ingredient</u>	<u>Weight Per Cent</u>
Ethyl alcohol	44.0
Laureth-4	0.5
30 Isopropyl alcohol	6.0
Cefoperazone	1.0
Purified water	balance

Citric acid can be used to adjust the pH to a desired level.

-56-

The composition in Example 52 contains approximately 1% Cefoperazone.

Other suitable compositions can be made in accordance with Example 52 which include

- 5 Cefoperazone in the following percentages: 0.5%, 2%, 3%, 4%, 5%, and 10%.

Example 53

A topical dermatological composition containing cefoperazone is obtained as follows.

- 10 Mix the following ingredients in the amounts specified.

<u>Ingredient</u>	<u>Weight Per Cent</u>
Ethyl alcohol	48.0
Laureth-4	0.5
15 Isopropyl alcohol	4.0
Propylene glycol	10.0
Cefoperazone	1.0
Purified water	balance

- 20 Citric acid can be used to adjust the pH to a desired level.

The composition in Example 53 contains approximately 1% Cefoperazone.

Other suitable compositions can be made in accordance with Example 53 which include

- 25 Cefoperazone in the following percentages: 0.5%, 2%, 3%, 4%, 5%, and 10%.

Example 54

A topical dermatological composition containing ampicillin is obtained as follows.

- 30 Mix the following ingredients in the amounts specified.

<u>Ingredient</u>	<u>Weight Per Cent</u>
Ethyl alcohol	48.0

-57-

	Laureth-4	0.5
	Isopropyl alcohol	4.0
	Propylene glycol	10.0
	Ampicillin	1.0
5	Purified water	balance

Citric acid can be used to adjust the pH to a desired level.

The composition in Example 54 contains approximately 1% Ampicillin.

- 10 Other suitable compositions can be made in accordance with Example 54 which include Ampicillin in the following percentages: 0.5%, 2%, 3%, 4%, 5%, and 10%.

Example 55

- 15 A topical dermatological composition containing amoxicillin is obtained as follows. Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
20	Ethyl alcohol	48.0
	Laureth-4	0.5
	Isopropyl alcohol	4.0
	Propylene glycol	10.0
	Amoxicillin	1.0
25	Purified water	balance

Citric acid can be used to adjust the pH to a desired level.

The composition in Example 55 contains approximately 1% Amoxicillin.

- 30 Other suitable compositions can be made in accordance with Example 55 which include Amoxicillin in the following percentages: 0.5%, 2%, 3%, 4%, 5%, and 10%.

-58-

Example 56

A topical dermatological composition containing ceftin is obtained as follows.

Mix the following ingredients in the amounts

5 specified.

Ingredient

Weight Per Cent

Ethyl alcohol 44.0

Laureth-4 0.5

Isopropyl alcohol 6.0

10 Ceftin 1.0

Purified water balance

Citric acid can be used to adjust the pH to a desired level.

The composition in Example 56 contains
15 approximately 1% Ceftin.

Other suitable compositions can be made in accordance with Example 56 which include Ceftin in the following percentages: 0.5%, 2%, 3%, 4%, 5%, and 10%.

20 Example 57

A topical dermatological composition containing ceftin is obtained as follows.

Mix the following ingredients in the amounts specified.

25 Ingredient

Weight Per Cent

Ethyl alcohol 48.0

Laureth-4 0.5

Isopropyl alcohol 4.0

Propylene glycol 10.0

30 Ceftin 1.0

Purified water balance

Citric acid can be used to adjust the pH to a desired level.

-59-

The composition in Example 57 contains approximately 1% Ceftin.

Other suitable compositions can be made in accordance with Example 57 which include Ceftin in 5 the following percentages: 0.5%, 2%, 3%, 4%, 5%, and 10%.

- For Examples 58-60, reference is made to U. S. Patent No. 4,497,794, incorporated herein by reference, in which topical gel compositions 10 containing the antibiotic erythromycin and benzoyl peroxide in a gel carrier are disclosed. A number of topical gel compositions of the present invention can be made by simply replacing the erythromycin disclosed in the gel compositions in 15 said patent with ampicillin, amoxicillin, or cephalosporin C, respectively, to provide topical gel compositions of the invention which contain benzoyl peroxide and the respective antibiotic of the invention.
- 20 The gel carrier or vehicle for Examples 58-60, prior to addition of the benzoyl peroxide and prior to addition of the respective antibiotic of the invention and, as explained below, the approximately 3 ml. of ethyl alcohol used to 25 dissolve the respective antibiotic for addition to the gel carrier to which benzoyl peroxide has been added, is comprised of the following ingredients in the approximate amounts specified.
- | 30 <u>Ingredient in gel carrier</u> | <u>Weight Percent</u>
<u>in the Final Mixture</u>
<u>containing antibiotic,</u>
<u>benzoyl peroxide, and</u>
<u>gel carrier</u> |
|-------------------------------------|---|
| 35 Butylated hydroxyanisole | 0.10 |
| Colloidal Bentonite | 2.50 |
| Carboxy vinyl polymer (acid form) | 1.00 |

-60-

Water, deionized or distilled	54.65
Diisopropanolamine	0.75
Ethyl alcohol	32.00
Diocetyl sodium sulfosuccinate	1.00

5 Example 58

A topical dermatological gel composition containing ampicillin antibiotic and benzoyl peroxide in a gel carrier or vehicle is obtained as follows.

10 To a first container add the benzoyl peroxide and the gel carrier or vehicle ingredients (approximately 5 grams of benzoyl peroxide and approximately 89 grams of gel carrier or vehicle). To a second container add powdered ampicillin
15 (approximately 3 grams of ampicillin). The contents of the first container and the contents of the second container are stable for long periods of time. When the topical composition containing ampicillin and benzoyl peroxide of the
20 invention is to be made, a quantity of 70% ethyl alcohol (e. g. 3 ml.) is added to the second container to dissolve the ampicillin and form an alcoholic solution thereof. Then the alcoholic solution of ampicillin is added to the first
25 container, and all the ingredients are mixed to form the topical gel composition of the invention which contains both ampicillin and benzoyl peroxide. This composition of the invention is stable, under refrigeration, for approximately 3
30 months.

More specifically, the blended topical gel composition of the invention with contains ampicillin and benzoyl peroxide in a gel carrier

-61-

or vehicle has the following components in the approximate amounts specified.

<u>Ingredient</u>	<u>Weight Per Cent</u>
ampicillin	3.0
5 Benzoyl peroxide	5.0
Gel carrier or vehicle	92.0

Citric acid can be used to adjust the pH to a desired level.

The composition in Example 58 contains 10 approximately 3% ampicillin.

Other suitable compositions can be made in accordance with Example 58 which include ampicillin in the following percentages: 0.5%, 1%, 2%, 4%, 5%, and 10%.

15 Example 59

A topical dermatological gel composition containing amoxicillin antibiotic and benzoyl peroxide in a gel carrier or vehicle is obtained as follows.

20 To a first container add the benzoyl peroxide and the gel carrier or vehicle ingredients (approximately 5 grams of benzoyl peroxide and approximately 89 grams of gel carrier or vehicle). To a second container add powdered amoxicillin 25 (approximately 3 grams of amoxicillin). The contents of the first container and the contents of the second container are stable for long periods of time. When the topical composition containing amoxicillin and benzoyl peroxide of the 30 invention is to be made, a quantity of 70% ethyl alcohol (e. g. 3 ml.) is added to the second container to dissolve the amoxicillin and form an alcoholic solution thereof. Then the alcoholic solution of amoxicillin is added to the first

-62-

container, and all the ingredients are mixed to form the topical gel composition of the invention which contains both amoxicillin and benzoyl peroxide. This composition of the invention is 5 stable, under refrigeration, for approximately 3 months.

More specifically, the blended topical gel composition of the invention with contains amoxicillin and benzoyl peroxide in a gel carrier 10 or vehicle has the following components in the approximate amounts specified.

<u>Ingredient</u>	<u>Weight Per Cent</u>
amoxicillin	3.0
Benzoyl peroxide	5.0
15 Gel carrier or vehicle	92.0

Citric acid can be used to adjust the pH to a desired level.

The composition in Example 59 contains approximately 3% amoxicillin.

20 Other suitable compositions can be made in accordance with Example 59 which include amoxicillin in the following percentages: 0.5%, 1%, 2%, 4%, 5%, and 10%.

Example 60

25 A topical dermatological gel composition containing cephalosporin C antibiotic and benzoyl peroxide in a gel carrier or vehicle is obtained as follows.

To a first container add the benzoyl peroxide 30 and the gel carrier or vehicle ingredients (approximately 5 grams of benzoyl peroxide and approximately 89 grams of gel carrier or vehicle). To a second container add powdered cephalosporin C (approximately 3 grams of cephalosporin C). The

-63-

contents of the first container and the contents of the second container are stable for long periods of time. When the topical composition containing cephalosporin C and benzoyl peroxide of 5 the invention is to be made, a quantity of 70% ethyl alcohol (e. g. 3 ml.) is added to the second container to dissolve the cephalosporin C and form an alcoholic solution thereof. Then the alcoholic solution of cephalosporin C is added to the first 10 container, and all the ingredients are mixed to form the topical gel composition of the invention which contains both cephalosporin C and benzoyl peroxide. This composition of the invention is stable, under refrigeration, for approximately 3 15 months.

More specifically, the blended topical gel composition of the invention with contains cephalosporin C and benzoyl peroxide in a gel carrier or vehicle has the following components in 20 the approximate amounts specified.

<u>Ingredient</u>	<u>Weight Per Cent</u>
cephalosporin C	3.0
Benzoyl peroxide	5.0
Gel carrier or vehicle	92.0

25 Citric acid can be used to adjust the pH to a desired level.

The composition in Example 60 contains approximately 3% cephalosporin C.

Other suitable compositions can be made in 30 accordance with Example 60 which include cephalosporin C in the following percentages: 0.5%, 1%, 2%, 4%, 5%, and 10%.

-64-

Example 61

A dermatological lotion containing amoxicillin is obtained by mixing the following ingredients in the amounts specified. The 5 ingredients in Container A is blended with the ingredients in Container B.

In Container A:

	<u>Ingredient</u>	<u>Weight Per Cent of ingredient in overall lotion</u>
10	Ethoxylated cetyl-stearyl alcohol	7.00
	Cetyl alcohol	0.75
	Isopropyl myristate	5.00
	Butylated hydroxyanisole	0.10
15	Polyoxyl 40 stearate	0.25
	Water, deionized or distilled	70.80
	Propylene glycol	3.00
	Acetone	7.00
	Diethyl sodium sulfosuccinate	0.10

20 In Container B:

	<u>Ingredient</u>	<u>Weight Per Cent of ingredient in overall lotion</u>
	Acetone	3.00
25	amoxicillin	3.00

Citric acid can be used to adjust the pH to a desired level.

To obtain the lotion composition in Example 61, the composition in Container A is prepared.

30 This composition in Container A is stable for long periods of time.

Container B can contain only amoxicillin for a long period of time. Just prior to forming the complete lotion composition, 3 grams of acetone

35 are added to Container B to dissolve the

-65-

amoxicillin. Then, the contents of Container A and Container B are combined to form the complete lotion composition of the invention.

The composition in Example 61 contains
5 approximately 3% amoxicillin.

Other suitable compositions can be made in accordance with Example 61 which include amoxicillin in the following percentages: 0.5%, 1%, 2%, 4%, 5%, and 10%.

10 Example 62

A dermatological lotion containing cephalosporin C is obtained by mixing the following ingredients in the amounts specified. The ingredients in Container A is blended with the
15 ingredients in Container B.

In Container A:

	<u>Ingredient</u>	<u>Weight Per Cent of ingredient in overall lotion</u>
20	Ethoxylated cetyl-stearyl alcohol	7.00
	Cetyl alcohol	0.75
	Isopropyl myristate	5.00
	Butylated hydroxyanisole	0.10
	Polyoxyl 40 stearate	0.25
25	Water, deionized or distilled	70.80
	Propylene glycol	3.00
	Acetone	7.00
	Diocetyl sodium sulfosuccinate	0.10

In Container B:

	<u>Ingredient</u>	<u>Weight Per Cent of ingredient in overall lotion</u>
30	Acetone	3.00
	cephalosporin C	3.00

-66-

Citric acid can be used to adjust the pH to a desired level.

To obtain the lotion composition in Example 62, the composition in Container A is prepared.

- 5 This composition in Container A is stable for long periods of time.

Container B can contain only cephalosporin C for a long period of time. Just prior to forming the complete lotion composition, 3 grams of 10 acetone are added to Container B to dissolve the cephalosporin C. Then, the contents of Container A and Container B are combined to form the complete lotion composition of the invention.

The composition in Example 62 contains 15 approximately 3% cephalosporin C.

Other suitable compositions can be made in accordance with Example 62 which include cephalosporin C in the following percentages: 0.5%, 1%, 2%, 4%, 5%, and 10%.

20 Example 63

A dermatological lotion is obtained by mixing the following ingredients in the amounts specified:

	<u>Ingredient</u>	<u>Weight Per Cent</u>
25	Ethoxylated cetyl-stearyl alcohol	7
	Cetyl alcohol	0.75
	Isostearyl neopentanoate	5
	Butylated hydroxyanisole	0.10
	Polyoxyl 40 stearate	0.25
30	Water, deionized or distilled	71.8
	Propylene glycol	3
	Acetone	10
	Diethyl sodium sulphosuccinate	0.1
	Ampicillin	2

-67-

Other suitable compositions can be made in accordance with Example 63 which include ampicillin in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

5 Example 64

A dermatological lotion is obtained by mixing the following ingredients in the amounts specified:

	<u>Ingredient</u>	<u>Weight Per Cent</u>
10	Ethoxylated cetyl-stearyl alcohol	7
	Cetyl alcohol	0.75
	Decyl oleate	5
	Butylated hydroxyanisole	0.10
	Polyoxyl 40 stearate	0.25
15	Water, deionized or distilled	71.8
	Propylene glycol	3
	Acetone	10
	Diethyl sodium sulphosuccinate	0.1
	Ampicillin	2
20	Other suitable compositions can be made in accordance with Example 64 which include ampicillin in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.	

Example 65

25 A lotion composition is obtained as follows. Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
	Ethoxylated cetyl-stearyl alcohol	7
30	Cetyl alcohol	0.75
	Isostearyl neopentanoate	5
	Butylated hydroxyanisole	0.10
	Polyoxyl 40 stearate	0.25

-68-

	Water, deionized or distilled	66.8
	Propylene glycol	3
	Benzoyl peroxide (micronized)	5
	Acetone	10
5	Dioctyl sodium sulphosuccinate	0.1
	Ampicillin	2

Other suitable compositions can be made in accordance with Example 65 which include ampicillin in the following percentages: 0.5%, 1% , 3%, 4%, 5%, and 10%.

Example 66

A lotion composition is obtained as follows.

Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
15	Ethoxylated cetyl-stearyl alcohol	7
	Cetyl alcohol	0.75
	Decyl oleate	5
	Butylated hydroxyanisole	0.10
20	Polyoxyl 40 stearate	0.25
	Water, deionized or distilled	66.8
	Propylene glycol	3
	Benzoyl peroxide (micronized)	5
	Acetone	10
25	Dioctyl sodium sulphosuccinate	0.1
	Ampicillin	2

Other suitable compositions can be made in accordance with Example 66 which include ampicillin in the following percentages: 0.5%, 1% , 3%, 4%, 5%, and 10%.

-69-

Example 67

A dermatological lotion is obtained by mixing the following ingredients in the amounts specified:

	<u>Ingredient</u>	<u>Weight Per Cent</u>
5	Ethoxylated cetyl-stearyl alcohol	7
	Cetyl alcohol	0.75
	Isostearyl neopentanoate	5
	Butylated hydroxyanisole	0.10
10	Polyoxyl 40 stearate	0.25
	Water, deionized or distilled	71.8
	Propylene glycol	3
	Acetone	10
	Dioctyl sodium sulphosuccinate	0.1
15	Amoxicillin	2

Other suitable compositions can be made in accordance with Example 67 which include amoxicillin in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

20 Example 68

A dermatological lotion is obtained by mixing the following ingredients in the amounts specified:

	<u>Ingredient</u>	<u>Weight Per Cent</u>
25	Ethoxylated cetyl-stearyl alcohol	7
	Cetyl alcohol	0.75
	Decyl oleate	5
	Butylated hydroxyanisole	0.10
	Polyoxyl 40 stearate	0.25
30	Water, deionized or distilled	71.8
	Propylene glycol	3
	Acetone	10
	Dioctyl sodium sulphosuccinate	0.1
	Amoxicillin	2

-70-

Other suitable compositions can be made in accordance with Example 68 which include amoxicillin in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

5 Example 69

A cream composition is obtained as follows. Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
10	Ethoxylated cetyl-stearyl alcohol	15
	Cetyl alcohol	1.25
	Isostearyl neopentanoate	5
	Butylated hydroxyanisole	0.10
	Polyoxyl 40 stearate	0.25
15	Water, deionized or distilled	57.30
	Propylene glycol	3
	Benzoyl peroxide (micronized)	5
	Acetone	10
	Diocetyl sodium sulphosuccinate	0.1
20	Ampicillin	3

Other suitable compositions can be made in accordance with Example 69 which include ampicillin in the following percentages: 0.5%, 1%, 2%, 4%, 5%, and 10%.

25 Example 70

A cream composition is obtained as follows. Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
30	Ethoxylated cetyl-stearyl alcohol	15
	Cetyl alcohol	1.25
	Decyl oleate	5
	Butylated hydroxyanisole	0.10

-71-

	Polyoxyl 40 stearate	0.25
	Water, deionized or distilled	57.30
	Propylene glycol	3
	Benzoyl peroxide (micronized)	5
5	Acetone	10
	Dioctyl sodium sulphosuccinate	0.1
	Ampicillin	3

Other suitable compositions can be made in accordance with Example 70 which include
 10 ampicillin in the following percentages: 0.5%, 1%, 2%, 4%, 5%, and 10%.

Example 71

A lotion composition is obtained as follows.
 Mix the following ingredients in the amounts
 15 specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
	Ethoxylated cetyl-stearyl alcohol	7
	Cetyl alcohol	0.75
	Isostearyl neopentanoate	5
20	Butylated hydroxyanisole	0.10
	Polyoxyl 40 stearate	0.25
	Water, deionized or distilled	66.8
	Propylene glycol	3
	Benzoyl peroxide (micronized)	5
25	Acetone	10
	Dioctyl sodium sulphosuccinate	0.1
	Amoxicillin	2

Other suitable compositions can be made in accordance with Example 71 which include
 30 amoxicillin in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

-72-

Example 72

A lotion composition is obtained as follows.

Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
5	Ethoxylated cetyl-stearyl alcohol	7
	Cetyl alcohol	0.75
	Decyl oleate	5
	Butylated hydroxyanisole	0.10
10	Polyoxyl 40 stearate	0.25
	Water, deionized or distilled	66.8
	Propylene glycol	3
	Benzoyl peroxide (micronized)	5
	Acetone	10
15	Diethyl sodium sulphosuccinate	0.1
	Amoxicillin	2

Other suitable compositions can be made in accordance with Example 72 which include amoxicillin in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

Example 73

A cream composition is obtained as follows.

Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
25	Ethoxylated cetyl-stearyl alcohol	15
	Cetyl alcohol	1.25
	Isostearyl neopentanoate	5
	Butylated hydroxyanisole	0.10
30	Polyoxyl 40 stearate	0.25
	Water, deionized or distilled	57.30
	Propylene glycol	3
	Benzoyl peroxide (micronized)	5
	Acetone	10

-73-

	Dioctyl sodium sulphosuccinate	0.1
	Amoxicillin	3

Other suitable compositions can be made in accordance with Example 73 which include

- 5 amoxicillin in the following percentages: 0.5%, 1%, 2%, 4%, 5%, and 10%.

Example 74

A cream composition is obtained as follows.

- Mix the following ingredients in the amounts
10 specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
	Ethoxylated cetyl-stearyl alcohol	15
	Cetyl alcohol	1.25
	Decyl oleate	5
15	Butylated hydroxyanisole	0.10
	Polyoxyl 40 stearate	0.25
	Water, deionized or distilled	57.30
	Propylene glycol	3
	Benzoyl peroxide (micronized)	5
20	Acetone	10
	Dioctyl sodium sulphosuccinate	0.1
	Amoxicillin	3

Other suitable compositions can be made in accordance with Example 74 which include

- 25 amoxicillin in the following percentages: 0.5%, 1%, 2%, 4%, 5%, and 10%.

Example 75

A lotion composition is obtained as follows.

- Mix the following ingredients in the amounts
30 specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
	Ethoxylated cetyl-stearyl alcohol	7
	Cetyl alcohol	0.75

-74-

	Isostearyl neopentanoate	5
	Butylated hydroxyanisole	0.10
	Polyoxyl 40 stearate	0.25
	Water, deionized or distilled	66.8
5	Propylene glycol	3
	Benzoyl peroxide (micronized)	5
	Acetone	10
	Diethyl sodium sulphosuccinate	0.1
	Cephalosporin C	2
10	Other suitable compositions can be made in accordance with Example 75 which include cephalosporin C in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.	

Example 76

15 A lotion composition is obtained as follows.

Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
	Ethoxylated cetyl-stearyl alcohol	7
20	Cetyl alcohol	0.75
	Decyl oleate	5
	Butylated hydroxyanisole	0.10
	Polyoxyl 40 stearate	0.25
	Water, deionized or distilled	66.8
25	Propylene glycol	3
	Benzoyl peroxide (micronized)	5
	Acetone	10
	Diethyl sodium sulphosuccinate	0.1
	Cephalosporin C	2

30 Other suitable compositions can be made in accordance with Example 76 which include cephalosporin C in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

-75-

Example 77

A cream composition is obtained as follows.

Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
5	Ethoxylated cetyl-stearyl alcohol	15
	Cetyl alcohol	1.25
	Isostearyl neopentanoate	5
	Butylated hydroxyanisole	0.10
10	Polyoxyl 40 stearate	0.25
	Water, deionized or distilled	57.30
	Propylene glycol	3
	Benzoyl peroxide (micronized)	5
	Acetone	10
15	Dioctyl sodium sulphosuccinate	0.1
	Cephalosporin C	3

Other suitable compositions can be made in accordance with Example 77 which include cephalosporin C in the following percentages:

20 0.5%, 1%, 2%, 4%, 5%, and 10%.

Example 78

A cream composition is obtained as follows.

Mix the following ingredients in the amounts specified.

	<u>Ingredient</u>	<u>Weight Per Cent</u>
25	Ethoxylated cetyl-stearyl alcohol	15
	Cetyl alcohol	1.25
	Decyl oleate	5
	Butylated hydroxyanisole	0.10
30	Polyoxyl 40 stearate	0.25
	Water, deionized or distilled	57.30
	Propylene glycol	3
	Benzoyl peroxide (micronized)	5
	Acetone	10

-76-

Dioctyl sodium sulphosuccinate	0.1
Cephalosporin C	3

Other suitable compositions can be made in accordance with Example 78 which include

- 5 cephalosporin C in the following percentages:
0.5%, 1%, 2%, 4%, 5%, and 10%.

Example 79

An oil-in-water emulsion containing amoxicillin in ointment form is obtained as

10 follows.

Part A is comprised of a 3.33% aqueous solution of amoxicillin.

Part B is an ointment base comprised of:

<u>Ingredient</u>	<u>Weight Per Cent</u>
15 viscid paraffin	35
white vaseline	35
cetylstearyl alcohol	30

- A mixture is obtained as follows. Mix 60 ml. of Part A is mixed with 40 ml. of Part B to 20 provide an oil-in-water emulsion in ointment form containing approximately 2% amoxicillin.

Other suitable compositions can be made in accordance with Example 79 which include amoxicillin in the following percentages: 0.5%,

25 1%, 3%, 4%, 5%, and 10%.

Example 80

A mineral-oil-based amoxicillin ointment is obtained as follows.

- Part A is comprised of a 6.66% aqueous 30 solution of amoxicillin.

Part B is an ointment base comprised of:

<u>Ingredient</u>	<u>Parts</u>
glycerin	5

-77-

isopropyl alcohol, 96%	5
mineral oil	60

- A mixture is obtained as follows. Mix 30 ml. of Part A with 70 ml. of Part B to provide a
- 5 mineral-oil-based ointment containing approximately 2% amoxicillin.

- Other suitable compositions can be made in accordance with Example 80 which include amoxicillin in the following percentages: 0.5%,
- 10 1%, 3%, 4%, 5%, and 10%.

Example 81

An oil-in-water emulsion containing cephalosporin C in ointment form is obtained as follows.

- 15 Part A is comprised of a 3.33% aqueous solution of cephalosporin C.

Part B is an ointment base comprised of:

<u>Ingredient</u>	<u>Weight Per Cent</u>
viscid paraffin	35
20 white vaseline	35
cetylstearyl alcohol	30

- A mixture is obtained as follows. Mix 60 ml. of Part A is mixed with 40 ml. of Part B to provide an oil-in-water emulsion in ointment form
- 25 containing approximately 2% cephalosporin C.

- Other suitable compositions can be made in accordance with Example 81 which include cephalosporin C in the following percentages: 0.5%, 1%, 3%, 4%, 5%, and 10%.

30 Example 82

A mineral-oil-based cephalosporin C ointment is obtained as follows.

-78-

Part A is comprised of a 6.66% aqueous solution of cephalosporin C.

Part B is an ointment base comprised of:

<u>Ingredient</u>	<u>Parts</u>
5 glycerin	5
isopropyl alcohol, 96%	5
mineral oil	60

A mixture is obtained as follows. Mix 30 ml. of Part A with 70 ml. of Part B to provide a 10 mineral-oil-based ointment containing approximately 2% cephalosporin C.

Other suitable compositions can be made in accordance with Example 82 which include cephalosporin C in the following percentages:

15 0.5%, 1%, 3%, 4%, 5%, and 10%.

A number of patients having acne vulgaris have been successfully treated with 2% topical ampicillin, and the case histories are described as follows.

20 Patient number one is a male and began treatment at the age of sixteen for acne vulgaris. Over the course of one year, he had been treated with the following agents in the order specified: first, retin-A and Benzamycin gel topically; 25 second, oral ampicillin in conjunction with topical erythromycin solution and topical retin-A (it is noted that therapeutic doses of oral ampicillin gave the patient diarrhea); third, low dose oral ampicillin (250 mgm per day) in 30 conjunction with topical retin-A and topical clindamycin solution; fourth, retin-A and clindamycin solution alone without any oral medication. Then the severity of the patient's acne worsened.

-79-

Then, photos were taken of the patient's right and left facial cheeks. The physical exam revealed on the face 2+ papules on a scale of 0-3+ and 2+ pustules on a scale of 0-3+. It is noted
5 that the scale used for describing the symptoms of acne herein is an adaptation of the scale described on page 611 of Bleicher, P., Charles, J., and Sober, A., "Topical Metronidazole Therapy for Rosacea", Arch Dermatol, 1987, vol. 123, pages
10 609-614.

At this point topical clindamycin was discontinued, and 2% ampicillin in a vehicle known as "Neutrogena Vehicle N (mild)" made by Neutrogena Dermatologics Division of Neutrogena
15 Corporation, Los Angeles Corporation, (which contains approximately: ethyl alcohol (41.5% by weight), Laureth (0.5% by weight), isopropyl alcohol (6.0% by weight), ampicillin (2.0% by weight), and purified water (50.0% by weight)) was
20 prescribed topically, in accordance with the invention, along with retin-A. Approximately seven weeks later, the patient subjectively indicated that his condition was improving. Also, at this time, a physical examination was
25 conducted which revealed on the face 1+ papules and only one pustule on the left cheek (0.5+ pustules). This constituted a 50% improvement over a period of seven weeks with the invention in contrast to negligible improvement with prior art
30 treatments over the course of more than one year. Photos were again taken.

The second patient is a female, and at the time of first treatment was 12 years old. She had acne vulgaris which was treated with the following
35 combinations of treatments over a two year period

-80-

in the order specified: first, a combination of topical retin-A and Benzamycin gel; second, oral ampicillin in conjunction with retin-A, topical clindamycin solution, and topical benzoyl

5 peroxide; third, topical clindamycin and topical retin-A and a 2% salicylic acid wash. At this point her acne vulgaris flared and on physical examination of her face, she had 2+ comedones on a scale of 0-3+, 2+ pustules on a scale of 0-3+, and
10 2+ papules on a scale of 0-3+.

At this point, photos were taken of her right and left facial cheeks. Then, in accordance with the invention, she was placed on 2% topical ampicillin (as described above in the treatment of
15 the first patient) twice daily to her face, and she continued with topical retin-A and salicylic acid wash.

Seven weeks later she was examined. The patient indicated that her acne cleared within a
20 two and one-half to three week period after commencing the treatment with topical ampicillin. On physical examination, her face revealed 1+ comedones, 0.5+ papules, and 0 pustules. The visual impression was a dramatic clearing
25 (approximately 75% reduction) of her acne vulgaris. Again, photos were taken. With the composition and method of the invention, there was a 75% improvement over a period of a mere seven weeks in contrast to prior art treatments over a
30 period of two years which resulted in only a negligible improvement. Photos were again taken.

The third patient is a female first seen by the inventor at age 28 for the treatment of acne vulgaris. Prior to seeing the inventor, over a
35 period of 12 years, she was treated for acne

-81-

vulgaris. Several months prior to seeing the inventor, for her facial acne, she was treated with topical retin-A, Benzamycin gel, and oral Bactrim (an oral sulfa drug whose generic name is 5 trimethoprim-sulfamethoxazole).

When the inventor first saw the third patient, she had 1+ comedones, 1+ pustules, and 1+ papules. The inventor prescribed oral ampicillin and continued the other topical medications. Upon 10 physical examination two months later, she had 1+ papules and 0+ comedones. She was improved.

This patient was to start taking a birth control pill (OrthoNovum, 1/35) for oral contraception. Due to the possible side effects 15 of oral antibiotic decreasing the effectiveness of the birth control pill, the inventor and the patient elected to stop the oral ampicillin. The patient was placed on topical benzoyl peroxide, topical clindamycin gel, and continued on topical 20 retin-A. Benzamycin gel was discontinued.

This patient was seen two months later, and upon physical examination, the patient exhibited 1+ comedones and 0.5+ papules. The patient was continued on the above-mentioned topical 25 medications; however, the retin-A strength was increased. The patient called the inventor approximately six weeks later to report that her acne vulgaris was flaring, and the inventor placed the patient on oral ampicillin; and the topical 30 medications were also continued.

This patient was seen by the inventor one month later and was noted, on physical examination, to have 2+ comedones and 2+ papules. At this point, the retin-A was increased to 0.1% 35 cream. All other topical medications were also

-82-

continued. The oral ampicillin was reduced to just one week out of the month.

Six weeks later, upon physical examination, this patient exhibited 2+ pustules, 0.5+ papules,

5 and 1+ comedones. The patient's acne was flaring. Again, due to the potential risk of decreasing the effectiveness of her oral contraceptive, the inventor wanted to discontinue the oral ampicillin and start her on a composition of the invention, 10 namely 2% topical ampicillin (as described above in the treatment of the first patient). A photo was taken prior to treatment with the topical ampicillin.

Upon treatment with the 2% ampicillin of the 15 invention, the topical clindamycin was discontinued. The topical retin-A and benzoyl peroxide were continued at their same doses.

Approximately seven weeks later, the patient remarked that her condition had improved with the 20 topical ampicillin. On physical examination, the patient had on her face, 0.5+ pustules on the right cheek and 0 pustules on the left cheek, 0.5+ papules, and 0.5+ comedones. The patient was approximately 50% improved clinically over the 25 last seven weeks. Due to the success of the topical ampicillin, the patient elected to continue topical ampicillin. The other topical medications (retin-A and benzoyl peroxide) were continued as well. Photos were again taken.

30 The fourth patient is a male and began treatment at age 12 for acne vulgaris. He was first treated with topical clindamycin gel and benzoyl peroxide. His acne vulgaris worsened by age 14 and required oral ampicillin 1 gram a day,

-83-

topical retin-A, and Benzamycin gel. The severity of the acne worsened so much by age 15 that oral ACCUTANE was discussed. The parents did not want to continue oral antibiotics or have their son
5 take ACCUTANE due to side effects.

Then, photos were taken of the patient's right and left facial cheeks. The physical exam revealed 2+ comedones, 1+ papules and 1+ pustules. In accordance with the invention, the patient was
10 started on topical 2% ampicillin (as described above in the treatment of the first patient) twice daily to his face, and continued on retin-A cream.

Approximately, 3 months later the patient returned. The patient indicated that his acne
15 improved within one month and cleared by two months time. The physical exam revealed 1+ comedones, 1 papule on his right cheek, 0+ papules on his left cheek (which is a score of 0.5+ papules), and 0+ pustules. This constituted a 75%
20 improvement over a period of twelve weeks with the invention in contrast to resistance to prior oral treatments over the course of three and one half years. Photos were again taken.

The fifth patient is male and began treatment
25 at age 12 for acne vulgaris. He had been treated with oral antibiotics including oral erythromycin, oral minocycline, topical retin-A, and benzoyl

-84-

peroxide lotion. He failed this treatment regimen due to severe acne vulgaris which necessitated treatment with oral ACCUTANE for 20 weeks. Even during his course of ACCUTANE, which is reserved
5 for severe acne unresponsive to oral antibiotics, he showed resistance and upon discontinuance of this oral agent he required oral ampicillin, and topical retin-A.

At age 14, 7 months off oral ACCUTANE the
10 patient's acne was worsening despite oral ampicillin 500 mg twice daily and topical retin-A cream. Then photos were taken of his facial cheeks and forehead. On physical exam on his forehead and facial cheeks were 2+ papules, 1+
15 pustules, and 2+ comedones. He was taken off of his oral ampicillin and in accordance with the invention he was placed on 2% topical ampicillin (as described above in the treatment of the first patient) twice daily to his face, and he was
20 continued on topical retin-A.

Approximately 12 weeks later the patient returned for examination. The patient indicated that he improved within the first few weeks of therapy but forgot to get a new 2% topical
25 ampicillin each month and used the same original topical ampicillin for the entire 3 months. On physical exam of his forehead and facial cheeks he

-85-

had 2+ comedones, 1+ pustules on his right cheek, 0.5+ pustules on his left cheek, and 1+ papules.

His acne was approximately 20% improved. The patient was educated to refill his prescription on

5 a monthly basis to achieve better efficacy. He was continued on his topical ampicillin and his topical retin-A was increased. Photos were taken for documentation of his forehead and facial cheeks.

10 The sixth patient is a female, and at the time of first treatment was 13 years old. She had acne vulgaris which was treated with topical retin-A, topical clindamycin, and oral minocycline. Her acne worsened and necessitated a
15 change from minocycline to oral ampicillin 1 gram a day, topical clindamycin, and topical retin-A. Her acne improved only minimally on oral ampicillin, and her mother was concerned about her continuing on high doses of oral ampicillin.

20 Photos were taken of the patient's face. At this point on physical exam her face revealed 2+ comedones, 1+ pustules, 1+ inflammatory papules. Then, in accordance with the invention, she was placed on 2% topical ampicillin (as described
25 above in the treatment of the first patient) twice daily to her face and she continued her oral

-86-

ampicillin and discontinued her topical clindamycin.

Approximately 7 weeks later she was examined. The patient indicated that her acne started to 5 clear within 2 weeks of commencing treatment with topical 2% ampicillin. On physical examination, her face revealed 1+ comedones, 0+ pustules, right cheek 0+ papules, left cheek 0.5+ papules. She was approximately 75% cleared from her previous 10 examination seven weeks prior. Photos were again taken.

The patients in these studies were all told to refill their topical ampicillin solution every one month and to keep their medication 15 refrigerated.

The table below (Table I) illustrates in summary form the six patients treated with the invention 2% topical ampicillin:

-87-

Table I Patients treated with topical ampicillin

Patient #'	Sex	Age Onset of Acne	Baseline exam face - start 2% top. ampicillin	Follow-up exam - face 2% top. ampicillin	Time in weeks between baseline exam and Follow Up exam
1	M	16	2+ papules 2+ pustules	1+ papules 0.5+ pustules	7 weeks
2	F	12	2+ papules 2+ pustules 2+ comedones	0.5+ papules 0+ pustules 1+ comedones	7 weeks
3	F	16	0.5+ papules 2+ pustules 1+ comedones	0.5+ papules 0.5+ pustules 0.5+ comedones	7 weeks
4	M	12	1+ papules 1+ pustules 2+ comedones	0.5+ papules 0+ pustules 1+ comedones	12 weeks
5	M	12	2+ papules 1+ pustules 2+ comedones	2+ papules 1+ pustules Right cheek 0.5+ pustules Left cheek 2+ comedones	12 weeks
6	F	13	1+ papules 1+ pustules 2+ comedones	0+ papules Right cheek 0.5+ papules Left cheek 0+ pustules 1+ comedones	7 weeks

From the description of the treatment of the patients and the composition examples set forth hereinabove, the weight percent of ethyl alcohol spans 35% to 98.5%. More specifically, the weight 5 percents of ethyl alcohol are as follows: 35.0% in Example 17; 35.0% in Example 16; 41.5% for the treated Patients; 41.0% in Example 1; 44.0% in Example 13; 48.0% in Example 54; 65% in Example 12; 71.2% in Example 3; and 98.5% in Example 12.

-88-

Similarly, from the description of the treatment of the patients and the composition examples set forth hereinabove, the weight percent of isopropyl alcohol spans 4% to 80%. More 5 specifically, the weight percents of isopropyl alcohol are as follows: 4.0% in Example 54; 4.3% in Example 25; 6.0% for the treated Patients; 6.0% in Exaple 13; and 80.0% in Example 39.

Similarly, from the description of the 10 treatment of the patients and the composition examples set forth hereinabove, the weight percent of propylene glycol spans 3% to 26.8%. More specifically, the weight percents of propylene glycol are as follows: 3.0% in Example 6; 3.0% in 15 Example 9; 3.0% in Example 30; 10.0% in Example 54; 10.0% in Example 39; and 26.8% in Example 3.

Similarly, from the description of the composition examples set forth hereinabove, the weight percent of glycerin is 6.9% in Example 25.

20 It is well known that ethyl alcohol, isopropyl alcohol, propylene glycol, and glycerin are water-miscible alcohols that can be applied topically to the skin.

It is seen in Example 12, that the carrier 25 ingredients for the antibiotic can be one water-miscible solvent (ethyl alcohol) without the presence of water. More generally, the lowest

-89-

weight percent for a water-miscible alcohol used in a carrier for the antibiotic is 3% as disclosed in Examples 6, 9 and 30 which disclose 3% propylene glycol.

5 It is seen in Example 3 that the carrier ingredients for the antibiotic can be two water-miscible solvents (ethyl alcohol and propylene glycol) without the presence of water.

It is seen in Examples 1, 14, 25, 39 and 54
10 that the carrier ingredients for the antibiotic can be two or more water-miscible solvents in the presence of water. The highest weight percent for two or more water-miscible solvents in the presence of water as carriers for the antibiotic
15 is 99.5% disclosed in Example 13.

Thus, the widest range for a water-miscible alcohol either alone, or in combination with another water-miscible alcohol or water, in weight percent, is 3% to 99.5%.

20 Similarly, from the description of the treatment of the patients and the composition examples set forth hereinabove, the sums of the weight percents of the water-miscible alcohols (ethyl alcohol, isopropyl alcohol, propylene
25 glycol, and glycerin) span 11.2% to 90%. More specifically, the sums of the weight percents of the water-miscible alcohols are as follows: 11.2%

-90-

in Example 25; 47.5% for the treated Patients; 50.0% in Example 13; 62.0% in Example 54; and 90.0% in Example 39.

Similarly, from the description of the treatment of the patients and the composition examples set forth hereinabove, the sums of the weight percents of the water-miscible alcohols (ethyl alcohol, isopropyl alcohol, propylene glycol, and glycerin) and water spans 42.4% to 99.5%. More specifically, the sums of the weight percents of the water-miscible alcohols and water are as follows: 42.2% in Example 25; 73.8% in Example 30; 74.8% in Example 9; 86.6% in Example 16; 90.0% in Example 17; 97.5% for the treated Patients; 98.0% in Example 6; 98.5% in Example 54; 99.0% in Example 39; and 99.5% in Example 13.

The foregoing description of the invention has been presented for purposes of illustration and description. It is not intended to be exhaustive or to limit the invention to the precise forms disclosed. Obvious modifications or variations of the methods and compositions of the invention are possible in light of the above teachings. The embodiments were chosen and described in order to best illustrate the principles of the invention and its practical application to thereby enable one of ordinary

-91-

skill in the art to best utilize the invention in various embodiments and with various modifications as are suited to the particular use contemplated.

It is intended that the

5 scope of the invention be defined by the claims appended hereto.

Claims

1. A method of treating a human being for acne and acneiform dermal disorders which comprises administering to the human being an amount of a composition consisting essentially of an antibiotic and a carrier, the composition applied topically directly to affected dermal tissues, the composition being effective to treat the acne and acneiform dermal disorders, wherein the antibiotic is selected from the group consisting of aminopenicillins and cephalosporins, and wherein the carrier includes at least one carrier ingredient selected from the group consisting of water and a water-miscible alcohol, wherein combined weight percents of said carrier ingredients is in a range spanning 3% to 99.5%.

2. The method described in claim 1 wherein the aminopenicillin is selected from the group consisting of ampicillin and amoxicillin, and derivatives and analogs thereof.

3. The method described in claim 1 wherein an aminopenicillin is selected from the group consisting of ampicillin and amoxicillin known by the following names: ampicillin; amoxicillin; bacampicillin; cyclacillin; ampicillin A; BRL 1341; P 50; Ay 6108; Adobacillin; Alpen; Amfipen;

Amphi-Bol; Bonapicillin; Grampenil; Guicitrina;
Copharcilin; Nuvapen; Synpenin; Viccillin;
Ultrabion; Ampipenin; Amplisom; Amimed; Ampi-
Penyl; Totalcicicina; Amipenix S; Amblosin;
Ampicin; Amplital; Astrapen; Binotal; Britacil;
Doktacillin; Marsilan; Pen-Bristol; Penbritin;
Penbrock; Penicline; Pentrex; Pentrexyl; Ponecil;
Polycillin; QI Damp; Toliocillin; Totacillin;
Totapen; ampicillin, monohydrate; ampicillin,
potassium salt; ampicillin, sesquihydrate;
ampicillin, trihydrate; ampicillin, anhydrous
form; ampicillin, sodium salt; ampicillin, D(-
) form, L(+) form, or DL-form; amoxycillin; AMPC;
Amolin; Amopenixin; Amoxi; Amoxipen; Anemolin;
Aspenil; Bristamox; Delacillin; Efpenix; Ibiamox;
Piramox; Sumox; amoxicillin; amoxicillin
trihydrate; amoxicillin hydrochloride trihydrate;
and amoxicillin beta-naphthalenesulfonate
trihydrate.

4. The method described in claim 1 wherein
the cephalosporin antibiotic is selected from the
group consisting of cephalosporin C; cephalosporin
C, sodium salt, dihydrate; cephalothin;
cephalothin, sodium salt (also known as Averon-1,
Cefalotin, Cephation, Ceporacin, Cepovenin,
Chephalotin, Coaxin, Keflin, Lospoven, Microtin,
Synclotin, and Toricelocin); cephapirin sodium;

cefadroxil; cefazolin; cephalexin; cephalothin; cephapirin; cephradine; cefaclor; cefamandole; cefonicid; ceforanide; cefotetan (a cephemycin); cefoxitin (a cephemycin); cefuroxime; cefoperazone; cefotaxime; ceftazidime; ceftin; ceftizoxime; the 1-acetyloxy ethyl ester of cefuroxime (cefuroxime axetil); ceftriaxone; and moxalactam (a 1-oxa-beta-lactam).

5. The method described in claim 1 wherein the antibiotic is an ampicillin.

6. The method described in claim 1 wherein the antibiotic is an amoxicillin.

7. The method described in claim 1 wherein the antibiotic is a cephalosporin.

8. The method described in claim 1 wherein the antibiotic is present in a range of from 0.5% to 10% by weight of the composition.

9. The method described in claim 1 wherein the antibiotic is applied in a carrier which includes at least one carrier ingredient selected from the group consisting of water and a water-miscible alcohol, wherein combined weight percents of said carrier ingredients is in a range spanning 3% to 99.5%.

10. The method described in claim 1 wherein the antibiotic is applied in a water-miscible

carrier including at least one water-miscible alcohol, wherein the weight percent of the at least one water-miscible alcohol is in a range spanning 11.2% to 90%.

11. The method described in claim 1 wherein the antibiotic is applied in a water-miscible carrier including at least two water-miscible alcohols, wherein the sum of the weight percents of the at least two water-miscible alcohols is in a range spanning 11.2% to 90%.

12. The method described in claim 1 wherein the antibiotic is present in an amount of 2% by weight and is applied in a carrier comprised of:

ethyl alcohol, 41.5% by weight,
Laureth-4, 0.5% by weight,
isopropyl alcohol, 6% by weight, and
water, 50% by weight.

13. A method of treating a human being for acne and acneiform dermal disorders which comprises administering to the human being an amount of an antibiotic selected from the group consisting of ampicillin, amoxicillin, and cephalosporin, and derivatives and analogs thereof, applied directly to affected dermal tissues, effective to treat the acne and acneiform dermal disorders, wherein the antibiotic is

applied in a carrier including at least one carrier ingredient selected from the group consisting of water and a water-miscible alcohol, wherein combined weight percents of said carrier ingredients is in a range spanning 3% to 99.5%.

14. The method described in claim 13 wherein the carrier is present in a weight percent range spanning 42.2% to 99.5%.

15. The method described in claim 13 wherein the carrier is present in a weight percent range spanning 42.2% to 99.5% and includes water, ethyl alcohol, and isopropyl alcohol.

16. The method described in claim 13 wherein the carrier includes ethyl alcohol in a weight percent range spanning 35% to 98.5%.

17. The method described in claim 13 wherein the carrier includes isopropyl alcohol in a weight percent range spanning 4% to 80%.

18. The method described in claim 13 wherein the carrier includes propylene glycol in a weight percent range spanning 3% to 26.8%.

19. The method described in claim 13 wherein the carrier includes water in a weight percent range spanning 9% to 95%.

20. The method described in claim 13 wherein the carrier includes at least one water-miscible

alcohol in a weight percent range spanning 11.2% to 90%.

21. The method described in claim 13 wherein the carrier includes water, at least one water-miscible alcohol, and mineral oil.

22. The method described in claim 13 wherein the carrier is present in a weight percent range spanning 42.2% to 99.5% and includes water in a weight percent range spanning 9% to 95%, ethyl alcohol in a weight percent range spanning 35% to 98.5%, and isopropyl alcohol in a weight percent range spanning 4% to 80%.

23. A method of treating a human being for acne and acneiform dermal disorders which comprises the step of:

topically administering to affected dermal areas of the human being an amount of a composition comprised of benzoyl peroxide and an antibiotic selected from the group consisting of aminopenicillins and cephalosporin and derivatives and analogs thereof, effective to treat the acne and acneiform dermal disorders, wherein the composition is applied in a carrier which includes at least one carrier ingredient selected from the group consisting of water and a water-miscible alcohol, wherein combined weight percents of said

carrier ingredients is in a range spanning 3% to 99.5%.

24. The method described in claim 23 wherein:

the antibiotic is present in a range spanning 0.5% to 10% by weight; and

the benzoyl peroxide is present in a range spanning 1% to 30% by weight.

25. The method described in claim 23 wherein the antibiotic is an aminopenicillin.

26. The method described in claim 23 wherein the aminopenicillin antibiotic is selected from the group consisting of ampicillin and amoxicillin.

27. The method described in claim 23 wherein the aminopenicillin antibiotic is an ampicillin.

28. The method described in claim 23 wherein the antibiotic is a cephalosporin.

29. A method of treating a human being for acne and acneiform dermal disorders which comprises administering to the human being an amount of a composition comprising an antibiotic, benzoyl peroxide, and a carrier, the composition applied topically directly to affected dermal tissues, the composition being effective to treat the acne and acneiform dermal disorders, wherein the antibiotic is selected from the group

consisting of aminopenicillins and cephalosporins, and wherein the carrier includes at least one carrier ingredient selected from the group consisting of water and a water-miscible alcohol, wherein combined weight percents of said carrier ingredients is in a range spanning 3% to 99.5%.

30. The method described in claim 29 wherein:

the antibiotic is present in an amount of 3% by weight;

the benzoyl peroxide is present in an amount of 5% by weight; and

the carrier is a gel vehicle present in an amount of 92% by weight.

31. The method described in claim 30 wherein the gel vehicle is comprised as follows:

<u>Ingredient in gel carrier</u>	<u>Weight Per Cent in the Final Mixture containing antibiotic, benzoyl peroxide, and gel carrier</u>
Butylated hydroxyanisole	0.10
Colloidal Bentonite	2.50
Carboxy vinyl polymer (acid form)	1.00
Water, deionized or distilled	54.65
Diisopropanolamine	0.75
Ethyl alcohol	32.00
Dioctyl sodium sulfosuccinate	1.00.

100

32. A pharmaceutical composition,
comprising:

an amount of an antibiotic selected from the group consisting of an aminopenicillin and a cephalosporin and derivatives and analogs thereof, effective to treat acne and acneiform dermal disorders in a human patient; and

a carrier for said antibiotic, said carrier suitable for topical application to dermal tissues, and said carrier is present in a weight percent range spanning 42.2% to 99.5% and includes water in a weight percent range spanning 9% to 95%, ethyl alcohol in a weight percent range spanning 35% to 98.5%, and isopropyl alcohol in a weight percent range spanning 4% to 80%.

33. The composition described in claim 32 wherein said antibiotic is present in an amount of 2% by weight and is present in a carrier comprised of:

ethyl alcohol, 41.5% by weight,
Laureth-4, 0.5% by weight,
isopropyl alcohol, 6% by weight, and
water, 50% by weight.

34. The composition described in claim 32 wherein said antibiotic is ampicillin.

35. A pharmaceutical composition,
comprising:

an amount of an antibiotic selected from the group consisting of an aminopenicillin and a cephalosporin and derivatives and analogs thereof, effective to treat acne and acneiform dermal disorders in a human patient;

an amount of a conventionally topically applied anti-acne medication selected from the

group consisting of benzoyl peroxide, sulfur, resorcinol, salicylic acid, and tretinoin; and a carrier for said antibiotic and said conventionally topically applied medication, said carrier suitable for topical application to dermal tissues, and said carrier being present in a weight percent range spanning 42.2% to 99.5% and said carrier including water in a weight percent range spanning 9% to 95%, ethyl alcohol in a weight percent range spanning 35% to 98.5%, and isopropyl alcohol in a weight percent range spanning 4% to 80%.

36. The composition described in claim 35 wherein said conventionally topically applied anti-acne medication is benzoyl peroxide.

37. A pharmaceutical composition, comprising:

an amount of an antibiotic selected from the group consisting of aminopenicillins and cephalosporins, and derivatives and analogs thereof, benzoyl peroxide, and a carrier, applied directly to affected dermal tissues, effective to treat the acne and acneiform dermal disorders, wherein:

the antibiotic is present in an amount of 3% by weight,

the benzoyl peroxide is present in an amount of 5% by weight, and

the carrier is a gel vehicle present in an amount of 92% by weight.

38. The composition described in claim 37 wherein the gel vehicle is comprised as follows:

<u>Ingredient in gel carrier</u>	<u>Weight Per Cent in the Final Mixture containing antibiotic, benzoyl peroxide, and gel carrier</u>
Butylated hydroxyanisole	0.10
Colloidal Bentonite	2.50
Carboxy vinyl polymer (acid form)	1.00
Water, deionized or distilled	54.65
Diisopropanolamine	0.75
Ethyl alcohol	32.00
Dioctyl sodium sulfosuccinate	1.00.

39. The composition described in claim 37
wherein the antibiotic is ampicillin.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US92/01405

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁸

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): A61K 31/43, 31/545

U.S. CL. 514/198, 200, 859

II. FIELDS SEARCHED

Minimum Documentation Searched ⁷

Classification System	Classification Symbols
U.S.	424/401; 514/198, 200, 859

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched ⁸III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	US, A, 4,444,755 (HORROBIN) 24 APRIL 1984 See column 2, line 64; column 3, line 28; column 6, line 19.	1-39
A	US, A, 4,954,487 (COOPER) 04 SEPTEMBER 1990 See the entire document.	1-39

¹⁰ Special categories of cited documents:

- ¹¹ "A" document defining the general state of the art which is not considered to be of particular relevance
- ¹² "E" earlier document but published on or after the international filing date
- ¹³ "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- ¹⁴ "O" document referring to an oral disclosure, use, exhibition or other means
- ¹⁵ "P" document published prior to the international filing date but later than the priority date claimed

¹⁶ "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention¹⁷ "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step¹⁸ "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.¹⁹ "&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

12 MAY 1992

Date of Mailing of this International Search Report

24 JUN 1992

International Searching Authority

ISA/US

Signature of Authorized Officer

G.S. Kishore

THIS PAGE BLANK (USPTO)

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

BLACK BORDERS

IMAGE CUT OFF AT TOP, BOTTOM OR SIDES

FADED TEXT OR DRAWING

BLURRED OR ILLEGIBLE TEXT OR DRAWING

SKEWED/SLANTED IMAGES

COLOR OR BLACK AND WHITE PHOTOGRAPHS

GRAY SCALE DOCUMENTS

LINES OR MARKS ON ORIGINAL DOCUMENT

REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY

OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)